Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

# und

# Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2020-B-179 Niraparib

Stand: August 2020

# I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Niraparib**
**[Erhaltungstherapie des Platin-sensiblen Rezidivs eines Ovarialkarzinoms, Eileiterkarzinoms oder einer primären Peritonealkarzinose]**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“. |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Nicht angezeigt. |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | **Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V**:<br>- Niraparib: Beschlüsse vom 02.04.2020<br>- Olaparib: Beschluss vom 06.12.2018<br>- Rucaparib: Beschluss vom 15.08.2019 |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | Siehe systematische Literaturrecherche |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Niraparib<br>L01XX54<br>Zejula® | Zugelassenes Anwendungsgebiet:<br>Zejula wird als Monotherapie zur Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden, angewendet. |
| Bevacizumab<br>L01XC07<br>Avastin® | Bevacizumab wird in Kombination mit Carboplatin und Gemcitabin oder in Kombination mit Carboplatin und Paclitaxel zur Behandlung von erwachsenen Patienten mit einem ersten platinsensitiven Rezidiv eines epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die zuvor noch nicht mit Bevacizumab oder mit anderen VEGF-Inhibitoren bzw. auf den VEGF-Rezeptor zielenden Substanzen behandelt wurden.<br>[…]<br><u>Behandlung des platinsensitiven Rezidivs:</u><br>Avastin wird entweder in Kombination mit Carboplatin und Gemcitabin über 6 und bis zu 10 Behandlungszyklen oder in Kombination mit Carboplatin und Paclitaxel über 6 und bis zu 8 Behandlungszyklen und in der Folge als Monotherapie bis zum Fortschreiten der Erkrankung angewendet. |
| Carboplatin<br>L01XA02<br>generisch | Carboplatin ist in der Behandlung folgender Karzinome angezeigt:<br>- Fortgeschrittenes epitheliales Ovarialkarzinom als<br>- First-Line Therapie<br>- Second-Line Therapie, wenn eine andere Behandlung nicht erfolgreich war<br>[…] |
| Cisplatin<br>L01XA01<br>Cisplatin Teva® | Cisplatin Teva wird angewendet zur Behandlung des:<br>- fortgeschrittenen oder metastasierten Ovarialkarzinoms<br>- […] |
| Cyclophosphamid<br>L01AA01<br>generisch | Cyclophosphamid ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt:<br>- Fortgeschrittenes Ovarialkarzinom |
| Doxorubicin<br>L01DB01 | - rezidivierendes Ovarialkarzinom<br>- […] |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Adrimedac | |
| Doxorubicin<br>L01DB01<br>Ribodoxo® | - fortgeschrittenes Ovarialkarzinom<br>- […] |
| Doxorubicin<br>*(liposomal)*<br>L01DB01<br>Caelyx® | Caelyx ist indiziert:<br>- Zur Behandlung von Patientinnen mit fortgeschrittenem Ovarialkarzinom nach Versagen einer platinhaltigen First-Line-Chemotherapie. |
| Epirubicin<br>L01DB03<br>Onkovis® | Epirubicin ist für die Behandlung folgender maligner Erkrankungen in Mono- und Kombinationsschemata angezeigt:<br>- fortgeschrittenes Ovarialkarzinom<br>- […] |
| Etoposid<br>L01CB01<br>Vepesid® | VEPESID K ist in Kombination mit anderen zugelassenen Chemotherapeutika angezeigt zur Behandlung des nicht-epithelialen Ovarialkarzinoms bei Erwachsenen. |
| Gemcitabin<br>L01BCO5<br>generisch | Gemcitabin ist in Kombination mit Carboplatin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem epithelialen Ovarialkarzinom, bei Patientinnen mit einem Rezidiv nach einer rezidivfreien Zeit von mindestens 6 Monaten nach einer platinbasierten Erstlinientherapie angezeigt. |
| Melphalan<br>01AA03<br>Melphalan-ratiopharm® | Melphalan-ratiopharm® wird in der konventionellen intravenösen Dosierung zur Behandlung des multiplen Myeloms und des Ovarialkarzinoms angewendet.<br>Melphalan-ratiopharm® kann in den oben genannten Anwendungsgebieten allein oder in Kombination mit anderen Zytostatika angewendet werden. |
| Niraparib<br>L01XX54<br>Zejula® | Zejula wird als Monotherapie zur Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden, angewendet. |
| Olaparib<br>L01XX46<br>Lynparza® | Lynparza wird angewendet als Monotherapie für die:<br>- Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines high-grade epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms, die auf eine Platin-basierte Chemotherapie ansprechen (vollständig oder partiell).<br>- […] |
| Paclitaxel | Ovarialkarzinom: |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| L01CD01<br>Paclitaxel<br>HAEMATO | Zur First-line Chemotherapie von Eierstockkrebs ist Paclitaxel HAEMATO 6 mg/ml bei Patientinnen mit fortgeschrittenem Eierstockkrebs oder einem Resttumor (>1 cm) nach vorausgegangener Laparotomie in Kombination mit Cisplatin indiziert.<br>Zur Second-line Chemotherapie von Eierstockkrebs ist Paclitaxel HAEMATO 6 mg/ml indiziert für die Behandlung von metastasierendem Ovarialkarzinom nach Versagen einer Standardtherapie mit Platin-haltigen Arzneimitteln. |
| Rucaparib<br>L01XX55<br>Rubraca® | Rubraca® ist indiziert als Monotherapie für die Erhaltungstherapie bei erwachsenen Patientinnen mit platinsensitivem, rezidiviertem, high-grade epithelialem Ovarial-, Eileiter- oder primärem Peritonealkarzinom, die nach platinbasierter Chemotherapie in Remission sind (vollständig oder partiell). |
| Topotecan<br>L01XX17<br>Topotecan medac | Als Monotherapie ist Topotecan angezeigt zur Behandlung von:<br>- Patientinnen mit metastasierendem Ovarialkarzinom nach Versagen einer Primär oder Folgetherapie.<br>- […] |
| Trabectedin<br>L01CX01<br>Yondelis | Yondelis in Kombination mit pegyliertem liposomalem Doxorubicin (PLD) wird angewendet bei Patientinnen zur Behandlung eines platinsensiblen Ovarialkarzinomrezidivs. |
| Treosulfan<br>L01AB02<br>Ovastat® | Ovastat 1000 (5000) mg ist allein oder in der Kombination mit anderen antineoplastisch wirksamen Substanzen angezeigt in der palliativen Therapie epithelialer Ovarialkarzinome der FIGO Stadien II – IV.<br>Eine Therapie mit Treosulfan allein (Monotherapie) ist angezeigt, wenn eine Kontraindikation gegen Cisplatin besteht. In allen anderen Fällen sollte Treosulfan mit Cisplatin kombiniert werden. |

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

# Vorgang: 2020-B-179 (Niraparib)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 28. Juli 2020 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| AOC | Advanced ovarian cancer |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| ECRI | ECRI Guidelines Trust |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| HR | Hazard Ratio |
| HRD | Homologous recombination deficiency |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| KI | Konfidenzintervall |
| LoE | Level of Evidence |
| NICE | National Institute for Health and Care Excellence |
| OC | Ovarian cancer |
| OR | Odds Ratio |
| ORR | Objective response rate |
| OS | Overall survival |
| PARP | Poly(ADP-ribose) polymerase |
| PC | Paclitaxel+carboplatin |
| PFS | Progression free survival |
| ROC | Recurrent ovarian cancer |
| RR | Relatives Risiko |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

# 1 Indikation

Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden, angewendet.

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Ovarialkarzinom, Eileiterkarzinom und primäres Peritonealkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.07.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1599 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 20 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# Ergebnisse

## 2.1 G-BA Beschlüsse/IQWiG Berichte

**G-BA, 2020 [3].**

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Niraparib (Neubewertung eines Orphan-Drugs nach Überschreitung der 50 Mio. Euro Grenze (Ovarialkarzinom, Eileiterkarzinom oder primäre Peritonealkarzinose; Erhaltungstherapie nach Zweitlinientherapie))

**Anwendungsgebiet (laut Zulassung vom 16. November 2017)**

Zejula wird als Monotherapie zur Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden, angewendet.

**Zweckmäßige Vergleichstherapie**

Olaparib oder beobachtendes Abwarten

**Ausmaß des Zusatznutzens von Niraparib gegenüber Olaparib:**

Ein Zusatznutzen ist nicht belegt.

**G-BA, 2019 [5].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. August 2019 - Rucaparib

**Anwendungsgebiet**

Rubraca ist indiziert als Monotherapie für die Erhaltungstherapie bei erwachsenen Patientinnen mit platinsensitivem, rezidiviertem, high-grade epithelialem Ovarial-, Eileiter- oder primärem Peritonealkarzinom, die nach platinbasierter Chemotherapie in Remission sind (vollständig oder partiell).

**Zweckmäßige Vergleichstherapie**

Olaparib oder Beobachtendes Abwarten

**Ausmaß des Zusatznutzens von Rucaparib gegenüber beobachtendem Abwarten:**

Ein Zusatznutzen ist nicht belegt.

**G-BA, 2018 [4].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Dezember 2018 - Olaparib

**Anwendungsgebiet**

Neues Anwendungsgebiet (laut Zulassung vom 08. Mai 2018):

Lynparza wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, basierte Chemotherapie ansprechen (vollständig oder partiell). eines high-grade epithelialen Ovarialkarzinoms, die auf eine Platin- basierte Chemotherapie ansprechen (vollständig oder partiell).

Hinweis:

Lynparza mit dem Wirkstoff Olaparib ist in unterschiedlichen Darreichungsformen verfügbar: Filmtabletten und Hartkapseln. Die Feststellungen dieses Beschlusses gelten für beide Darreichungsformen.

Erwachsene Patientinnen mit einem Platin-sensitiven Rezidiv eines high-grade epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms, die auf eine Platin-basierte Chemotherapie ansprechen (vollständig oder partiell).

**Vergleichstherapie**

Beobachtendes Abwarten

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

Anhaltspunkt für einen geringen Zusatznutzen.

## 2.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

## 2.3 Systematische Reviews

**Ruscito I et al., 2020 [12].**

Incorporating Parp-inhibitors in Primary and Recurrent Ovarian Cancer: A Meta-analysis of 12 phase II/III randomized controlled trials

**Fragestellung**

Aim of the present meta-analysis is to analyze and pool current available results obtained with PARPi, administered alone or in combination with chemo- and/or target-therapies, in terms of efficacy and safety, for the treatment of both recurrent and primary advanced ovarian cancer patients, in order to define the exact benefit added by this class of drugs, establish the subgroup of patients, who could most benefit from their use and possibly reinforce current evidence supporting the extension of PARPi license in both primary and recurrent disease setting.

**Methodik**

Population:

- primary or recurrent ovarian cancer

Intervention:

- PARPi compound alone or in combination with chemotherapy and/or target therapies

Komparator:

- placebo/chemotherapy alone/target therapy alone

Endpunkte:

- PFS, toxicity (nausea, vomitting, fatigue, diarrhoe, abdominal pain, anemia, neutropenia, thrombocytopenia, hypertension)

Recherche/Suchzeitraum:

- PubMed, Embase and Scopus, December 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 13 studies (reporting results from 12 trials) (N=5171)

Charakteristika der Population:

- All eligible studies reported the prognostic effect of a PARPi treatment alone or in association with chemotherapy or target therapy vs control in terms of PFS [5–8,16–18,21–26]. Results were grouped for disease setting (platinum- sensitive recurrent vs primary ovarian cancer).

Qualität der Studien:

| ¤ | SELECTION· BIAS¤ | PERFORMANCE·¶ BIAS¤ | DETECTION· BIAS¤ | ATTRITION·¶ BIAS¤ | REPORTING· BIAS¤ | OTHER·¶ BIAS¤ |
|---|---|---|---|---|---|---|
| LEDERMANN·2012¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| LIU·2014¤ | +¤ | -¤ | -¤ | +¤ | +¤ | +¤ |
| OZA·2015¤ | +¤ | -¤ | -¤ | +¤ | +¤ | +¤ |
| KUMMAR·2015¤ | +¤ | -¤ | -¤ | +¤ | +¤ | +¤ |
| MIRZA·2016¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| PUJADE-LAURAINE·2017¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| COLEMAN·2017¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| MOORE·2018¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| MIRZA·2019¤ | +¤ | -¤ | -¤ | +¤ | +¤ | +¤ |
| GONZALÉZ-MARTÍN·2019¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| RAY-COQUARD·2019¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |
| COLEMAN·2019¤ | +¤ | +¤ | +¤ | +¤ | +¤ | +¤ |

**Studienergebnisse:**

PARPi as maintenance therapy in recurrent, platinum-sensitive ovarian cancer

- PARP-inhibitors vs placebo
  - 4 studies: 1677 platinum-sensitive recurrent ovarian cancer patients were included
  - Pooled HR on global population (independently from BRCA and/or HRD status) showed that PARPi treatment, compared to Placebo, significantly improves patients' PFS (HR 0.37; 95% CI: 0.32–0.42; P < 0.00001, fixed effects model)
  - Pooled HR was also stratified basing on germline/somatic BRCA mutational status ad/or HRD status. Considering only the population with known positive germline and/or somatic BRCA mutation, the effect of PARPi on patients' prognosis was even greater (HR 0.29; 95% CI: 0.23–0.37; P < 0.00001, fixed effects model Fig. 2b), as well as in patients with HRD positive tumors (HR 0.34; 95% CI: 0.27–0.43; P < 0.00001, fixed effects model Fig. 2c).
  - Less marked, although still greatly significant, the effect of PARPi treatment on BRCA wild-type patients' PFS (HR 0.45; 95% CI: 0.35–0.57; P < 0.00001, fixed effects model Fig. 2d).
- Combination PARPi and cytotoxic chemotherapy
  - 237 patients, enrolled in two different randomized controlled trials [16,22] were included into this analysis. 118 patients received a PARPi plus chemotherapy until disease progression or unacceptable toxicity, whereas 119 women were treated with chemotherapy alone.
  - Pooled HR on global population showed that adding PARPi to standard chemotherapy treatment significantly improves patients' PFS independently from their BRCA and/or HRD status (HR 0.50; 95% CI: 0.33–0.74; P = 0.0007, fixed effects model Fig. 3a).
- Combination PARPi and anti-angiogenesis

- 187 patients, who participated in two separated randomized controlled trials [21,26] were included into this analysis. 92 patients received a PARPi (Olaparib or Niraparib) plus target therapy (Bevacizumab or Cediranib) until disease progression or unacceptable toxicity and 95 patients received PARPi alone.
- Pooled HR on global population showed that the addition of Bevacizumab or Cediranib to PARPi treatment resulted in a significant improvement of patients' PFS independently from their BRCA and/or HRD status (HR 0.38; 95% CI: 0.26–0.55; P < 0.00001, fixed effects model

Adverse events

- Parp-inhibitors vs placebo
  - among all gastrointestinal, hematological and fatigue symptoms, only anemia accounted for severe occurrence in patients with recurrent or primary ovarian cancer treated with PARPi rather than placebo (OR 10.51; 95% CI: 5.27–20.96; P < 0.00001, fixed effects model).
- Parp-inhibitors + chemotherapy vs chemotherapy
  - Pooled data showed that severe anemia (OR 1.55; 95% CI: 1.17–2.05; P < 0.002, random effects model and fatigue (OR 1.80; 95% CI: 1.00–3.25; P=0.05, random effects model Fig. 9c) were more frequently observed in patients administered with PARPi and chemotherapy compared to women subjected to chemotherapy alone.
  - Nausea (OR 1.96; 95% CI: 1.00–3.84; P = 0.05, fixed effects model
- Parp-inhibitors + target-therapy vs Parp-inhibitors alone
  - Severe hypertension occurrence could be observed more frequently in recurrent OC patients subjected to PARPi combined with Bevacizumab or Cediranib compared with PARPi alone (OR 11.03; 95% CI: 1.42–85.92; P = 0.02, fixed effects model).

[16] Kummar S, Oza AM, Fleming GF, et al. Randomized trial of oral cyclophosphamide and veliparib in high-grade serous ovarian, primary peritoneal, or fallopian tube cancers, or BRCA-mutant ovarian cancer. Clin Cancer Res 2015;21:1574–82.
[17] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinumsensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–92.
[18] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014;15:852–61.
[21] Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurren platinum-sensitive ovarian cancer: a randomized phase 2 study. Lancet Oncol 2014;15:1207–14.
[22] Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol 2015;16:87–97.
[23] Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinumsensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154–64.
[24] Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949–61.
[25] Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274–84.
[26] Mirza MR, Åvall Lundqvist E, Birrer MJ, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGOAVANOVA2/ ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Onco 2019;20:1409–19.

**Anmerkung/Fazit der Autoren**

In conclusion, this meta-analysis shows that PARPi are a valid option for the treatment of both primary and relapsed ovarian cancer patients, with a relative low incidence of severe side effects. In addition, these results could help in defining more appropriate control arms in future randomized clinical trials involving PARPi.

*Kommentare zum Review*

Einschluss von Studien mit zum Teil nicht zugelassenen AM

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**Ruiz-Schutz VC et al., 2019 [11].**

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

**Fragestellung**

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

**Methodik**

Population:

- Advanced cancer

Intervention:

- olaparib

Komparator:

- placebo, chemotherapy, abiraterone or other therapies, OS, PFS

Endpunkte:

- all-grade and high-grade fatigue and anemia adverse events

Recherche/Suchzeitraum:

- Pubmed/Medline, Embase and Cochrane Library through January 2000 to June 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 9 RCTs (4 RCTs: ovarian cancer, 2 RCTs: gastric cancer, 1 RCT mCRPC, 1 RCT NSCLC)

Charakteristika der Population:

In two trials, both in ovarian cancer, randomization was between placebo/control and olaparib (Ledermann et al., 2014; Pujade- Lauraine et al., 2017) or chemotherapy/control and olaparib. (Robson et al., 2017; Kaye et al., 2012) In three studies, olaparib was combined to cytotoxic chemotherapy, (Bang et al., 2015, 2017; Oza et al., 2015)

Qualität der Studien:

- Using the Cochrane Collaboration tool for risk of bias classification, we found the quality of the included studies to be generally good and fair.

**Studienergebnisse:**

OS and PFS

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

| Author, year | Phase | Histology | Patients enrolled | Treatment arms | Median age, years (range) | Median treatment duration, months (range) | Median OS, months (95% CI) | Median PFS, months (95% CI) | Patients for analysis | Jadad score |
|---|---|---|---|---|---|---|---|---|---|---|
| (2018) | | | | Gemtuzumab 250 mg QD + Olaparib 200 mg BID | 65 (39-85) | NR | 23.5 (18.2-28.4) | 12.8 (9.1-14.7) | 91 | |
| Kaye et al. (2012) | 2 | Ovarian cancer (BRCA1/2 positive) | 97 | PLD 50 mg/m2 q4w | 53 (43-81) | NR | NR | 7.1 (3.7-10.7) | 32 | 3 |
| | | | | Olaparib 200 mg QD | 58.5 (45-77) | NR | NR | 6.5 (5.5-10.1) | 32 | |
| | | | | Olaparib 400 mg QD | 53.5 (35-76) | NR | NR | 8.8 (5.4-9.2) | 32 | |
| Lederman et al. (2014) | 2 | Ovarian cancer | 326 | Placebo | 59 (33-84) | 4.7 (1.1-13.8) | 27.8 (24.4-34.0) | 4.8 (4.0-5.5) | 128 | 5 |
| | | | | Olaparib 400 mg BID | 58 (21-89) | 6.9 (0.1-15.6) | 29.8 (27.1-35.7) | 8.4 (7.4-11.5) | 136 | |
| Oza et al. (2015) | 2 | Ovarian cancer | 173 | Carboplatin + Paclitaxel[b] | 62 (31-79) | 7.5 (IQR 4.3-9.8) | 37.6 (27.8-44.6) | 9.6 (9.1-9.7) | 75 | 3 |
| | | | | Carboplatin + Paclitaxel + Olaparib[c] | 59 (27-78) | 9.8 (IQR 7.1-13.9) | 33.8 (26.9-38.5) | 12.2 (9.7-15.0) | 81 | |
| Pujade-Lauraine et al. (2017) | 3 | Ovarian cancer | 295 | Placebo | 56 (IQR 49-63) | 5.6 (NR-NR) | Not reached | 5.5 (5.2-5.8) | 99 | 5 |
| | | | | Olaparib 300 mg BID | 56 (IQR 51-63) | 19.4 (NR-NR) | Not reached | 19.1 (16.3-25.7) | 195 | |
| Robson et al. (2017) | 3 | Breast cancer | 302 | Standard chemotherapy[d] | 45 (24-68) | 3.4 (0.7-23.0) | 19.6 (NR-NR) | 3.8 (NR-NR) | 91 | 3 |
| | | | | Olaparib 300 mg BID | 44 (22-76) | 8.2 (0.5-28.7) | 19.3 (NR-NR) | 7.8 (NR-NR) | 205 | |

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

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

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

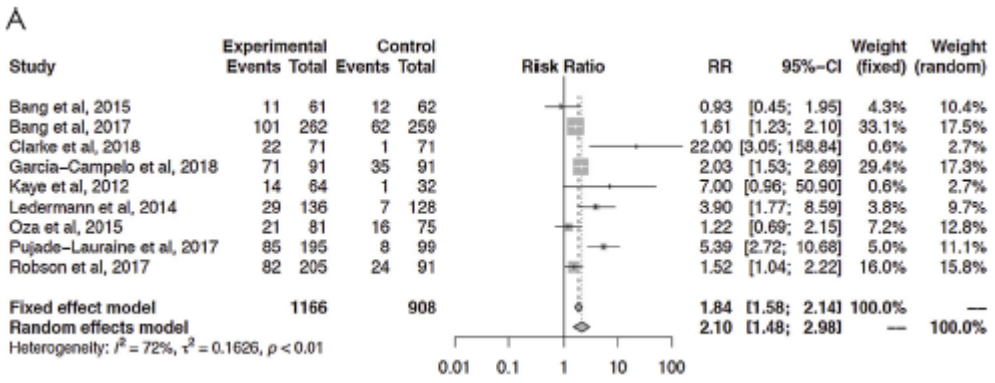
[c] Carboplatin AUC4 + Paclitaxel 175 mg/m2, q3w. In the combination phase, Olaparib was administered with 200 mg BID on days 1–10, every 3 weeks. In the maintenance phase, Olaparib was administered with 400 mg BID, continuously.

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

Adverse events

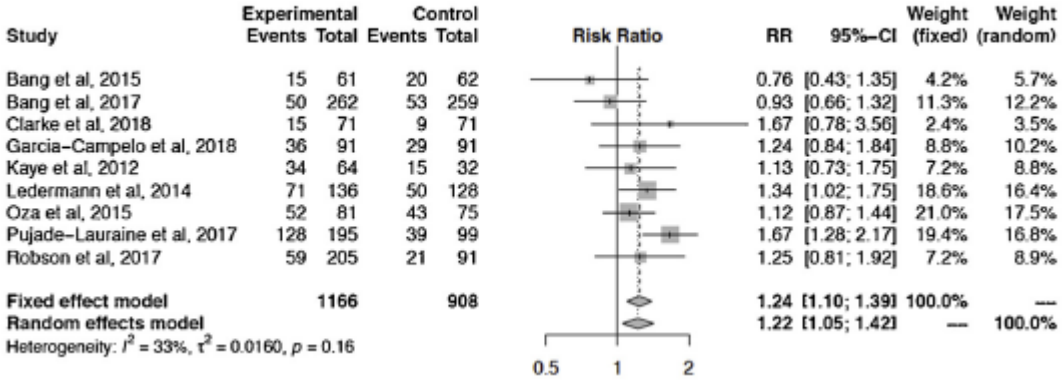
- The RR of all-grade and high fatigue was 1.24 (95% CI, 1.10–1.39) and 1.71 (95% CI, 1.06–2.77), respectively.
- The RR of all-grade and high-grade anemia was 2.10 (95% CI, 1.48–2.98) and 3.15 (95% CI, 1.73–5.71), respectively.

All grade anemia



All-grade fatigue

A




→ *Poolen von Studien mit unterschiedlichen Indikationen (Ovarialkarzinom und Nicht-Ovarialkarziom)*

Kaye, S.B., Lubinski, J., Matulonis, U., et al., 2012. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1
or BRCA2 mutations and recurrent ovarian cancer. J. Clin. Oncol. 30, 372–379
Ledermann, J., Harter, P., Gourley, C., et al., 2014. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 15, 852–861
Oza, A.M., Cibula, D., Benzaquen, A.O., et al., 2015. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 16, 87–97.
Pujade-Lauraine, E., Ledermann, J.A., Selle, F., et al., 2017. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 18, 1274–1284.

**Anmerkung/Fazit der Autoren**

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

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**Tomao F et al., 2019 [16].**

Parp inhibitors as maintenance treatment in platinum sensitive recurrent ovarian cancer: An updated meta-analysis of randomized clinical trials according to BRCA mutational status

**Fragestellung**

The aim of this meta-analysis is to investigate the effectiveness of PARPis as maintenance treatment in platinum sensitive recurrent ovarian cancer (ROC) by paying particular attention to the population's BRCA status of mutation and stratifying results into five different categories: whole population, germ-line BRCA mutated patients, somatic BRCA mutated patients, patients with HRD and wild type population

**Methodik**

Population:

- patients affected by platinum-sensitive ROC

Intervention:

- PARPis were used in a maintenance setting after a platinum based chemotherapy

Komparator:

- placebo

Endpunkte:

- PFS

Recherche/Suchzeitraum:

- PubMed, Medline, Scopus, EMBASE and clinicaltrials.gov up to May 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias

**Ergebnisse**

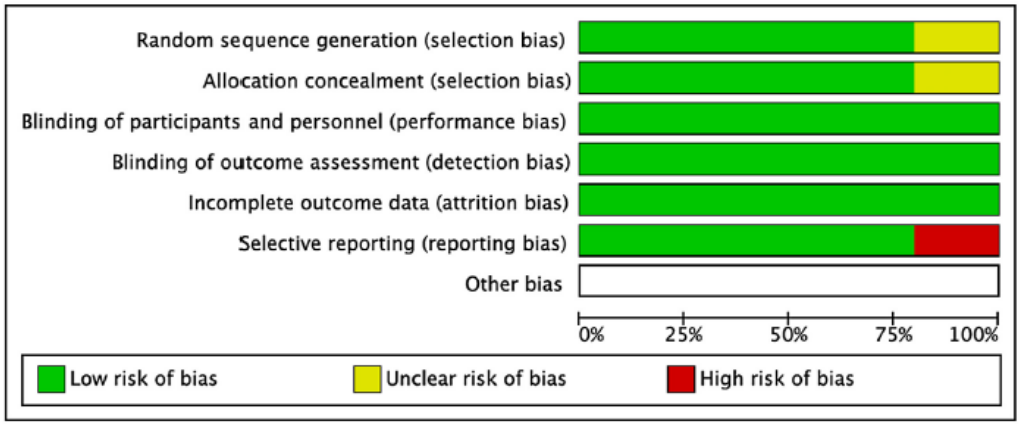
Anzahl eingeschlossener Studien:

- 4 RCTs (N=1677)

Charakteristika der Population:

- Median age of patients was similar among all studies. As expected, in the studies that reported age by mutational status. Most of the studies included both mutated and not mutated patients; only the SOLO 2 trial included exclusively BRCA mutated population

Qualität der Studien:



**Studienergebnisse:**

PFS

Table 2
PFS according to the BRCA mutational status.

| Author, Year, Study | Whole population<br>Nr. of patients *<br>HR 95% [CI] | BRCA1-2 mutated population<br>Nr. of patients *<br>HR 95% [CI] | BRCA1-2 somatic mutated population<br>Nr. of patients*<br>HR 95% [CI] | HRD positive population<br>Nr. of patients*<br>HR 95% [CI] | Wild-type population<br>Nr. of patients *<br>HR 95% [CI] |
|---|---|---|---|---|---|
| Lederman et al, 2012 [15]<br>STUDY 19 | 136 vs 129<br>0.35 [0.25, 0.49] | | | | |
| Lederman et al, 2014 [16]<br>STUDY 19 | | 74 vs 62<br>0.18 [0.10, 0.32] | | | 57 vs 61<br>0.54 [0.34, 0.85] |
| Mirza et al, 2016 [18]<br>NOVA | not reported | 138 vs 65<br>0.27 [0.17, 0.42] | 35 vs 12<br>0.27 [0.08, 0.91] | 106 vs 56<br>0,38 [0.24–0.59] | 234 vs 116<br>0.45 [0.34, 0.60] |
| Pujade-Lauraine et al, 2017 [17]<br>SOLO 2 | | 196 vs 99<br>0.30 [0.22, 0.41] | | | |
| Coleman et al, 2017 [19]<br>ARIEL 3 | 375 vs 189<br>0.36 [0.29, 0.44] | 130 vs 66<br>0.23 [0.16, 0.34] | 40 vs 16<br>0.23 [0.10, 0.53] | 236 vs 118<br>0.32 [0.24–0.42] | High LOH<br>106 vs 52<br>0.44[0.29, 0.66]<br>Low LOH<br>107 vs 54<br>0·58 [0·40–0·85] |

* PARPis vs Placebo; HR = hazard ratio; CI = confidence intervals; LOH = loss of heterozygosity.

[15] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366(15):1382–92.
[16] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014;15(8):852–61.
[17] Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a doubleblind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18(9):1274–84.
[18] Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375(22):2154–64.
[19] Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390(10106):1949–61.

**Anmerkung/Fazit der Autoren**

The results of this meta-analysis confirm the effectiveness of PARPis in improving PFS when administered to germinal or somatic BRCA mutated patients, in a maintenance setting, in platinum sensitive ROC, after a good response to the last platinum-based chemotherapy. These data partially support the concept that it is exactly due to synthetic lethality that PARPis are particularly effective in BRCA mutated patients.

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**Yi T et al., 2019 [20].**

Antitumor efficacy of PARP inhibitors in homologous recombination deficient carcinomas

**Fragestellung**

Thus, the objective of this study was to perform a systematic review and meta-analysis to evaluate the clinical benefit of PARPis, mainly focused on: (1) comparing the differences in efficacy of PARPis in HRD population vs. non-HRD population; (2) analyzing the differential clinical benefit of PARPis in BRCA mutant HRD vs. BRCA wild type HRD subpopulations.

**Methodik**

Population:

- treatment for patients with cancer

Intervention/ Komparator:

- PARP is as a single agent or combined with other regimens

Endpunke:

- OS, PFS

Recherche/Suchzeitraum:

- April 20, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 13 studies (n = 2,592 participants)
  - 8 RCTs and 5 Phase II trials
  - **ovarian carcinoma trials (n = 8)** and nonovarian carcinoma trials (n = 6, breast cancer: 1 study, gastric cancer: 2 studies, colorectal cancer: 2 studies, and prostate cancer: 1 study)

Charakteristika der Population:

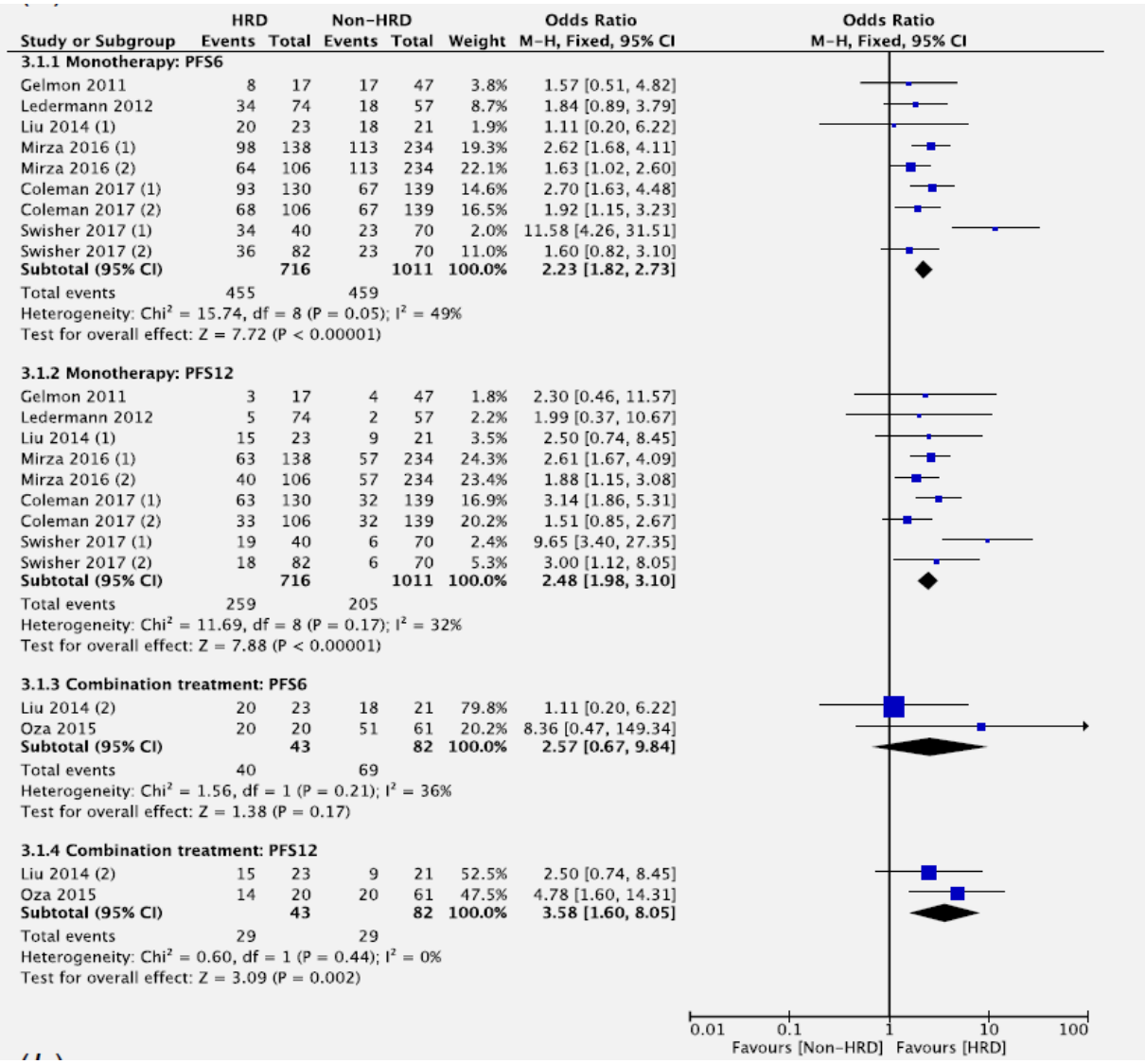
- All clinical trials were international multi-center studies, with intervention group sample sizes ranging from 10 to 431 patients.Qualität der Studien:
- In the interventional arm, PARPis being investigated as monotherapy were: olaparib in 7 studies, rucaparib in 2 studies, and niraparib in 1 study. The combination therapy regimens included olaparib plus cediranib (1 study), olaparib plus paclitaxel (2 study), olaparib plus paclitaxel plus carboplatin (1 study) and veliparib plus temozolomide (1 study). One study17 in particular reported PARPis in 2 treatment arms, olaparib alone vs. olaparib plus cediranib. All patients recruited in the trials had been pre-treated with standard chemotherapy.

Table 1. Characteristics of included studies for PARP inhibitors

| Study (Year) | Clinical Trials.gov, number | Phase | Study design | Cancer type | Treatment | Total no. of patients | HR gene mutation status (n) | No. of patients in each cohorts | Age (years), median (range) | Endpoints |
|---|---|---|---|---|---|---|---|---|---|---|
| **Ovarian cancer trials** | | | | | | | | | | |
| Gelmon *et al.* (2011)[9] | NCT00679783 | II | Single-arm | Ovarian cancer | Olaparib | 64 | BRCA mutation[1] | 17 | 58 (39–84) | PFS, OS |
| | | | | | | | *BRCA* wild-type or unknown | 47 | 47 (24–80) | |
| Ledermann *et al.* (2012),[8] 2014)[16] | NCT00753545 | II | RCT | Ovarian cancer | Olaparib | 265 | *BRCA* mutation[1] | 96 | 58.0 (21–89) | PFS, OS |
| | | | | | Placebo | | *BRCA* wild-type or unknown | 169 | 59.0 (33–84) | |
| Liu *et al.* (2014)[17] | NCT01116648 | II | RCT | Ovarian cancer | Olaparib | 90 | *gBRCA* mutation | 47 | 58.1 (32.7–81.9) | PFS, OS |
| | | | | | Olaparib+cediranib | | *gBRCA* wild-type or unknown | 43 | 57.8 (41.9–85.6) | |
| Oza *et al* (2015)[18] | NCT01081951 | II | RCT | Ovarian cancer | Olaparib+ paclitaxel+ carboplation | 162 | *gBRCA* mutation | 24 | 59 (27–78) | PFS, OS |
| | | | | | Paclitaxel+ carboplation | | *gBRCA* wild-type | 138 | | |
| Mirza *et al.* (2016)[19] | NCT01847274 | III | RCT | Ovarian cancer | Niraprib | 553 | *gBRCA* mutation | 138 | 57.4 (36–83) | PFS |
| | | | | | Placebo | | *gBRCA* wild-type with HRD | 106 | 62 (33–84) | |
| | | | | | | | *gBRCA* wild-type without HRD | 234 | | |
| Coleman *et al.* (2017)[20] | NCT01968213 | III | RCT | Ovarian cancer | Rucaparib | 564 | *BRCA* mutation[1] | 130 | 61.0 (53.0–67.0) | PFS, OS |
| | | | | | Placebo | | *BRCA* wild-type with high-LOH | 106 | 62.0 (53.0–68.0) | |
| | | | | | | | *BRCA* wild-type with low-LOH | 139 | | |
| Pujade-Lauraine *et al.* (2017)[21] | NCT01874353 | III | RCT | Ovarian cancer | Olaparib | 294 | *gBRCA* mutation | 195 | 56 (51–63) | PFS, OS |
| | | | | | Placebo | | | | 56 (49–63) | |
| Swisher *et al.* (2017)[11] | NCT01891344 | II | Single-arm | Ovarian cancer | Rucaparib | 204 | *BRCA* mutation[1] | 40 | 58.5 (53.5–67.5) | PFS |
| | | | | | | | *BRCA* wild-type and LOH high | 82 | 65.0 (58.0–71.0) | |
| | | | | | | | *BRCA* wild-type and LOH low | 70 | 65.0 (55.0–72.0) | |

**Studienergebnisse:**

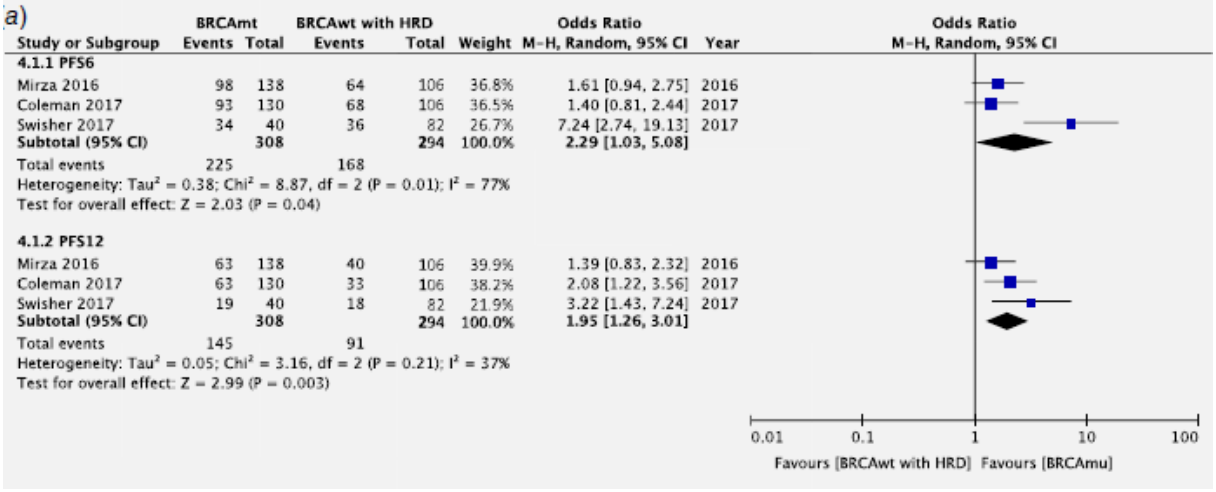
PFS at 6 months (PFS6) and at 12 months (PFS12): Effect of PARP inhibitors as monotherapy or combination therapy




Forest plots of pooled analyses for the effect of PARP inhibitors as monotherapy or combination therapy for HRD vs. non-HRD on progression-free survival, stratified by ovarian or nonovarian carcinoma. Three studies (Mirza et al. 2016, Coleman et al. 2017, and Swisher et al. 2017) used twice in the pooled analysis as each study included two HRD cohorts (BRCA mutated HRD and BRCA wild-type HRD) and one non-HRD cohort (BRCA wild-type without HRD). With non-HRD subgroup serving as a control, comparisons between HRD and non-HRD were conducted twice: (1) "BRCA mutated HRD" vs. "BRCA wild-type without HRD"; (2) "BRCA wild-type HRD" vs. "BRCA wild-type without HRD".[…] As the width of the diamond indicates the 95% CI, the narrower diamonds have more reliable results. Note: Liu 2014 (1) used PARPis as monotherapy; Liu 2014 (2) used PARPis as combination therapy. Abbreviation: PARPi(s), PARP inhibitor(s); HRD, homologous recombination deficiency; PFS6/12, progression-free survival rates at 6/12 months; OS12/24, overall survival rates at 12/24 months.

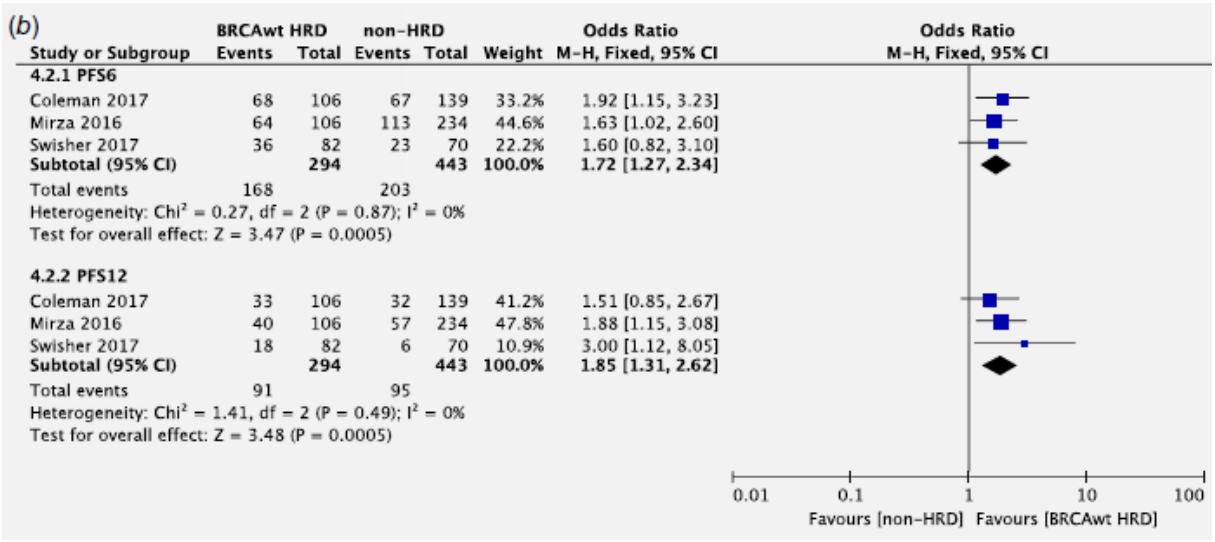
BRCA mutation vs. BRCA wild-type

- BRCA mutation subgroup compared to the BRCA wild-type HRD subgroup: The Odds ratio (OR) PFS6 and ORPFS12 were 2.29 (95% CI: 1.03–5.08) and 1.95 (95% CI: 1.26–3.01), respectively




<u>HRD vs. non-HRD subgroup</u>

- Strikingly, there were significant differences in PFS6 and PFS12 when comparing the BRCA wild-type HRD to the non-HRD subgroup. The ORPFS6 and ORPFS12 were 1.72 (95% CI: 1.27–2.34) and 1.85 (95% CI: 1.31–2.62), respectively




9. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852–61.
11. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017;18:75–87.
16. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014;15:852–61.
17. Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014;15:1207–14.
18. Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol 2015;16:87–97.
19. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154–64.
20. Coleman RL, Oza AM, Lorusso D, et al. Rucapar maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949–61.
21. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274–84.

**Anmerkung/Fazit der Autoren**

Our study demonstrated that the therapeutic efficacy of PARP inhibitors goes beyond germline and somatic BRCA mutations and that it may be more widely applicable to carcinomas with defects in other HR DNA repair genes. In patients with BRCA wild-type HRD carcinomas, significant PFS advantage was achieved when compared to non-HRD patients. Therefore, additional HRD genes could be utilized as novel biomarkers for the identification of patients who may benefit from targeted therapy using PARPis. As the list of carcinogenesis associated HRD genes expands, genetic testing for HRD-related gene panels should be considered for routine clinical practice.

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**Ma J et al., 2019 [10].**

Efficacy and safety of olaparib maintenance therapy in platinum-sensitive ovarian cancer patients with BRCA mutations: a meta-analysis o randomized controlled trials

**Fragestellung**

We assessed the efficacy and safety of olaparib maintenance therapy on platinum-sensitive ovarian cancer patients with BRCA mutations through a meta-analysis of available randomized controlled trials (RCTs) to provide more evidence for its clinical applications.

**Methodik**

Population:

- patients older than 18 years of age with BRCA mutations ovarian cancer, which had received at least two previous courses of platinum-based chemotherapy regimen

Intervention:

- olaparib

Komparator:

- placebo or other chemotherapy drugs

Endpunkte:

- a) PFS, b) overall survival (OS), c) quality of life, and d) adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, Wanfang, CNKI, Web of Science, Cochrane Library, and VIP databases from 1 August 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

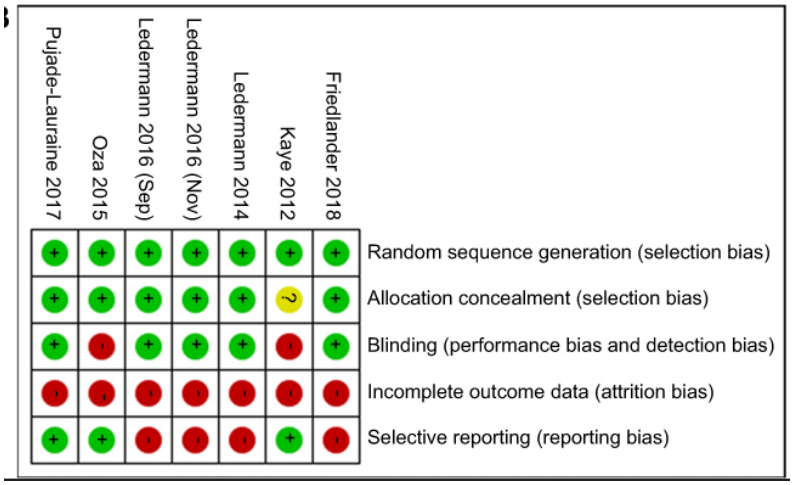
Anzahl eingeschlossener Studien:

- 4 RCTs

Charakteristika der Population:

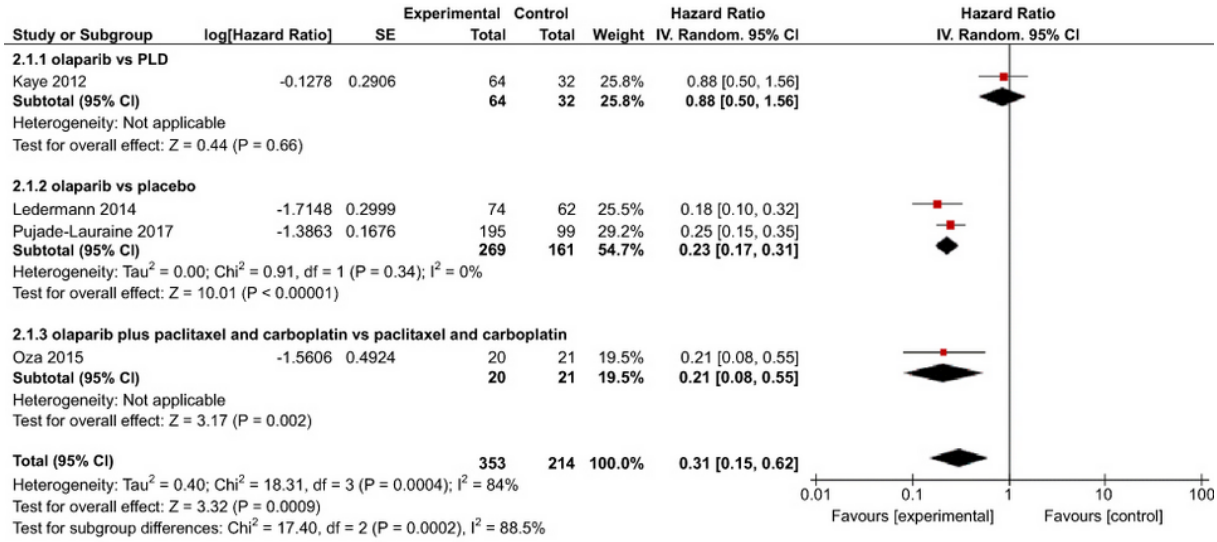
- Kaye 2012 was a multicenter, randomized, and open-label Phase II study. It enrolled 96 patients with histologically or cytologically confirmed BRCA-mutated recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma and assigned them to receive olaparib (200 or 400 mg twice daily) or PLD (50 mg/m2).
- The trial reported by Ledermann 2014, 2016 (September) and 2016 (November) was a multicenter, randomized, and double-blind Phase II study. It divided 264 patients (including 136 cases with BRCA mutations and 128 cases with wild-type BRCA) with recurrent ovarian, fallopian tube cancer, or primary peritoneal cancer into two groups receiving olaparib (400 mg twice daily) or placebo, respectively. Patients had received two or more previous lines of platinum-based chemotherapy.
- Oza 2015 conducted a multicenter, open-label Phase II study which enrolled 156 patients (including 41 patients with BRCA mutations) with histologically or cytologically diagnosed platinum-sensitive ovarian cancer, including primary peritoneal and fallopian tube cancers. Patients had received a maximum of three previous lines of platinum-based chemotherapy.
- Pujade-Lauraine 2017 and Friedlander 2018 were both international, multicenter, double-blind, randomized, placebo-controlled, Phase III studies. Two hundred and ninety-four patients with BRCA mutations were histologically confirmed relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer. Patients had received at least two previous lines of platinum-based chemotherapy.

Qualität der Studien:

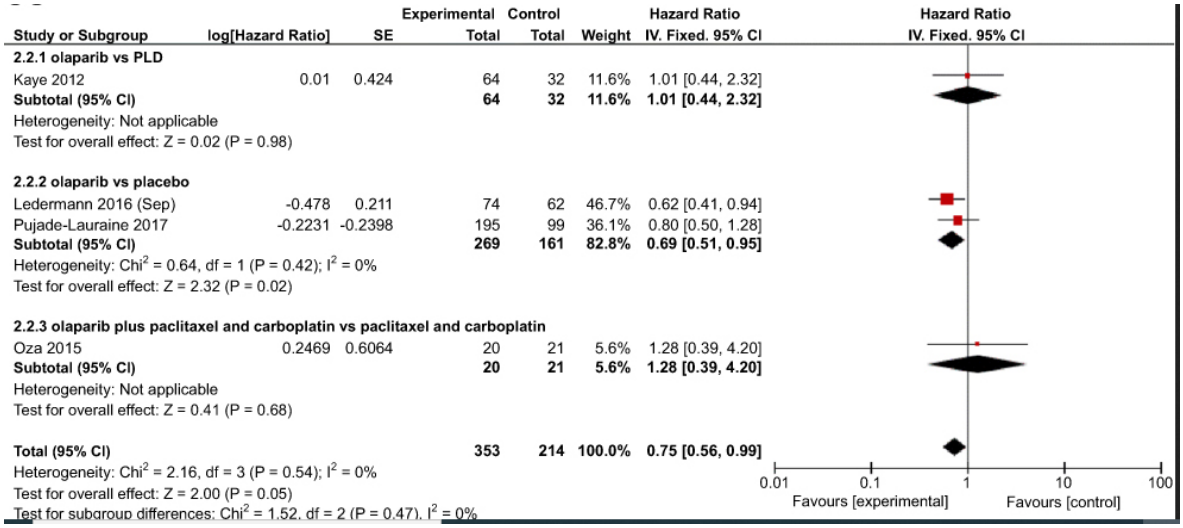


**Studienergebnisse:**

Progression-free survival (PFS)




Overall survival




Quality of life

- Three trials reported quality of life in olaparib-treated ovarian cancer patients with BRCA mutations (n=526).
- Two trials found no statistical difference in the total FACT-O score between olaparib and placebo groups (Ledermann 2016 [November], OR=1.38, 95% CI=0.58–3.39, P=0.47; Friedlander 2018, mean −0.03 points, P=0.98). In another trial (Kaye 2012), a higher improvement was noted for olaparib compared with PLD for the total FACT-O score (OR=7.23, 95% CI=1.09–143.3, P=0.039).

Adverse events (Olaparib compared with other treatments)

- Anemia

- Grade 1–2: RR=4.42, 95% CI=2.27–8.60, P<0.0001; grade 3–4: RR=7.63, 95% CI=2.57–22.67, P=0.0003.
- Heterogeneity in anemia (grade 1–2: P=0.92, I2=0%; grade 3–4: P=0.91, I2=0%)

- Fatigue:
  - Grade 1–2: RR=2.08, 95% CI=1.48–2.93, P<0.0001, fixed-effect model) and high-grade vomiting presented no difference (grade 3–4: RR=1.97, 95% CI=0.50–7.80, P=0.33, fixed-effect model)
  - Heterogeneity (grade 1–2: P=0.21, I2=37.4%; grade 3–4: P=0.28, I2=15.6%)
- Vomiting
  - Grade 1–2: RR=2.08, 95% CI=1.48–2.93, P<0.0001, fixed-effect model); grade 3–4: RR=1.97, 95% CI=0.50–7.80, P=0.33, fixed-effect model)
  - Heterogeneity: grade 1–2: P=0.21, I2=37.4%; grade 3–4: P=0.28, I2=15.6%
- Diarrhea
  - Low-grade: RR=1.46, 95% CI=1.06–2.03, P=0.02, fixed-effect model), high-grade (grade 3–4): RR=0.76, 95% CI=0.21–2.71, P=0.67, fixed-effect model, n=526).
  - Heterogeneity: Grade 3–4 diarrhea (P=0.10, I2=63.4%); grade 1–2 diarrhea (P=0.43, I2=0%)
- Nausea
  - Low-grade: RR=1.87, 95% CI=1.33–2.63, P=0.0004).
  - Heterogeneity: Low-grade nausea (grade 1–2: P=0.02, I2=81.7%); high-grade nausea (grade 3–4: P=0.22, I2=33.8%)
- Constipation
  - No statistically significant difference for olaparib compared with other interventions in overall analysis (RR=0.92, 95% CI=0.50–1.70, P=0.80, random-effect model; RR=0.43, 95% CI=0.01–13.85, P=0.63, random-effect model).
  - Heterogeneity: grade 1–2: P=0.04, I2=76.0%; grade 3–4: P=0.10, I2=63.3%
- Abdominal pain
  - Grade 1–2: RR=0.82, 95% CI=0.61–1.11, P=0.20, fixed-effect model; Grade 3–4: RR=0.55, 95% CI=0.20–1.54, P=0.26, fixed-effect model).
  - Heterogeneity (grade 1–2: P=0.76, I2=0%; grade 3–4: P=0.91, I2=0%)

23. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 2012;30(4):372–379. doi:10.1200/JCO.2011.36.9215
24. Ledermann J, Harter P, Gourley C, et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. Br J Cancer. 2016;115(11):1313–1320. doi:10.1038/ bjc.2016.348
25. Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomized phase 2 trial. Lancet Oncol. 2015;16(1):87–97.
26. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomized, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274–1284.

**Anmerkung/Fazit der Autoren**

As evidenced from our pooled data from 567 patients examined in our review, olaparib maintenance therapy (mostly administered orally at the dose of 400 mg) was as effective and well tolerated as other therapies with respect to efficacy (mainly measured by PFS, OS, and quality of life) and adverse events. There was high-quality evidence that women with different types of ovarian cancer who received olaparib had significant improvements in PFS. Moreover,

we considered that olaparib slightly prolonging OS in patients belonged to moderate-quality evidence. Related to seven adverse events, the evidence ranged from moderate to high quality.

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**Staropoli N et al., 2018 [15].**

The Era of PARP inhibitors in ovarian cancer: “Class Action” or not? A systematic review and meta-analysis

**Fragestellung**

In order to assess by aggregate analysis the overall impact of PARPis in the management of EOC patients, we performed a systematic review of literature and we estimated this effect by a meta-analytic approach.

**Methodik**

Population:

- patients with diagnosis of EOC

Intervention:

- PARPi-based schedule

Komparator:

- a conventional placebo maintenance

Endpunkte:

- PFS and toxicities

Recherche/Suchzeitraum:

- between January 2008, year of introduction of PARPis in clinical trials, and April 2018.

Qualitätsbewertung der Studien:

- Cochrane reviewers’ handbook

**Studienergebnisse**

Anzahl eingeschlossener Studien:

- N=5 (n=1839)

Charakteristika der Population:

Table 1
Main characteristics of the randomized trials included in the meta-analysis. Abbreviations: overall survival, OS; progression free survival, PFS; response rate, RR; hazard ratio, HR.

| TRIALS (First author) | YEAR | TREATMENT ARMS | TARGETED PATHWAY | PLATINUM STATUS | BRCA | PATIENTS | RR Control arm | RR Experimental arm | OS | PFS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | HR | HR |
| Ledermann J | 2014 | Olaparib vs Placebo | PARP inhibitor | sensitive | unselected | 265 | 129 | 136 | 0.73 | 0.35 |
| Ledermann J | 2014 | Olaparib vs Placebo | PARP inhibitor | sensitive | wt | 118 | 61 | 57 | 0.83 | 0.54 |
| Ledermann J | 2014 | Olaparib vs Placebo | PARP inhibitor | sensitive | mt | 136 | 62 | 74 | 0.62 | 0.18 |
| Oza A | 2014 | Olaparib plus CHT vs CHT | PARP inhibitor | sensitive | unselected | 162 | 81 | 81 | 1.17 | 0.51 |
| Oza A | 2014 | Olaparib plus CHT vs CHT | PARP inhibitor | sensitive | mt | 41 | 21 | 20 | 1.28 | 0.21 |
| Pujade-Lauraine E | 2017 | Olaparib vs Placebo | PARP inhibitor | sensitive | mt | 295 | 99 | 196 | | 0.3 |
| Coleman RL | 2017 | Rucaparib vs Placebo | PARP inhibitor | sensitive | unselected | 564 | 189 | 375 | | 0.36 |
| Coleman RL | 2017 | Rucaparib vs Placebo | PARP inhibitor | sensitive | mt | 196 | 66 | 130 | | 0.23 |
| Coleman RL | 2017 | Rucaparib vs Placebo | PARP inhibitor | sensitive | wt | 368 | 132 | 245 | | 0.32 |
| Mirza M.R. | 2017 | Niraparib vs placebo | PARP inhibitor | sensitive | mt | 203 | 65 | 138 | | 0.27 |
| Mirza M.R. | 2017 | Niraparib vs placebo | PARP inhibitor | sensitive | wt | 350 | 116 | 234 | | 0.45 |

Qualität der Studien:

- All 6 trials involved, were scored A (low risk of bias)

**Studienergebnisse:**

OS

- Regarding the survival outcome only the PFS analyses were evaluable for retrievable data.

PFS

- Although a significant advantage was showed in all subgroups, both in unselected setting (pooled HR 0.38 95%CI 0.32 - 0.46) and in BRCAwt patients (pooled HR 0.41 95%CI 0.31 - 0.55), we demonstrated that the most evident benefit of PARPis is retained in the BRCAmut population (pooled HR 0.25 95%CI 0.21 - 0.31). In particular, in this analysis the potential better performance seems to be evident for olaparib.
- The indirect comparison results indicated the lack of significant differences between the different PARPis.

Indirect comparison of treatments. Abbreviations: progression free survival, PFS; hazard ratio, HR; confidence interval, CI.

| | Olaparib 150 mg bid | Rucaparib 600 mg | Niraparib |
|---|---|---|---|
| Olaparib 400 mg | HR (CI) 0.6 (0.315 - 1.144) p- value 0.121 | HR (CI) 0.749 (0.394 - 1.423) p-value 0.377 | HR (CI) 0.667 (0.326 - 1.365) p-value 0.268 |
| Rucaparib 600 mg | HR (CI) 1.248 (0.809 - 1.927) p-value 0.316 | | |
| Niraparib | HR (CI) 1.111 (0.648 - 1.905) p-value 0.702 | | |

Toxicity analyses

PARPis Toxicities in all grades and 3–4 grade/SAE subgroup.

| ALL GRADES | Olaparib RR (CI) | Rucaparib RR (CI) | Niraparib RR (CI) |
|---|---|---|---|
| Abdominal Pain | 0,7 (0,47–1,11) | 114 (0,86–152) | 076 (0,57–1,03) |
| Constipation | 1,24 (0,6–1,87) | 152 (114–2,03) | 198 (144–2,72) |
| Diarrea | 1,62 (092–2,34) | 145 (1,06–198) | 092 (065–1,32) |
| Fatigue | 1,66 (1,18–2,04) | 157 (1,32–1,87) | 144 (1,18–1,74) |
| Nausea | 2,27 (1,67–252) | 205 (1,68–2,49) | 209 (1,7–2,57) |
| Vomiting | 1,94 (1,31–3,31) | 245 (1,7–353) | 212 (1,48–304) |
| Anemia | 5,37 (2,27–9,39) | 637 (3,54–11,47) | 748 (4,29–13,04) |
| **SEVERE** | | | |
| Abdominal Pain | 0,84 (0,15–3,11) | 454 (0,58–35,54) | 065 (0,15–2,87) |
| Constipation | 0,07 (0,05–45,34) | 178 (0,37–8,41) | 098 (0,09–10,69) |
| Diarrea | 2,54 (0,12–37,40) | 050 (0,07–353) | 024 (0,02-2,67) |
| Fatigue | 2,02 (0,58–8,14) | 252 (098–6,48) | 1463 (201-106,44) |
| Nausea | 5,58 (0,3–93,63) | 706 (0,93–53,25) | 268 (0,60–11,97) |
| Vomiting | 2,53 (0,33–23,53) | 378 (0,87–16,36) | 341 (0,42–27,54) |
| Anemia | 9,60 (1,93–44,73) | 3528 (4,94–252,01) | 9147 (5,71–1464,79) |

**Anmerkung/Fazit der Autoren**

We conclude that the efficacy class effect does not justify expanded market approval for any of PARPis and suggest that differences in safety profile should be the major issue in drug choice.

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**Guo XX et al., 2018 [6].**

The efficacy and safety of olaparib in the treatment of cancers: a meta-analysis of randomized controlled trials

**Fragestellung**

We thus performed this meta-analysis of all published Phase II–III randomized controlled trials (RCTs) to evaluate the efficacy and safety of olaparib in the treatment of various advanced or metastatic cancers.

**Methodik**

Population:

- cancer patients

Intervention/ Komparator:

- olaparib containing therapy or control (placebo or chemotherapy)

Endpunkte:

- PFS, OS, ORR, AE

Recherche/Suchzeitraum:

- PubMed and Embase from January 2000 to January 2018

Qualitätsbewertung der Studien:

- Jadad scale

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 8 RCTs (n=1957), of whom 786 had ovarian cancer[7,18–20], 302 breast cancer, 649 gastric cancer, and 220 small-cell lung cancer (SCLC).

Charakteristika der Population:

**Table 1** Baseline characteristics of the eight randomized controlled trials included in the meta-analysis

| | Phase | Underlying malignancy | Treatment arm | Control arm | Patients enrolled | Age (years), median (range) | Median OS (months) | Median PFS (months) | Jadad score |
|---|---|---|---|---|---|---|---|---|---|
| **Oza et al[20]** | II | OC | Olaparib 200 mg twice daily plus PC | PC | 162 | 59.0 (27–28) | 33.8 | 12.2 | 3 |
| **Kaye et al[19]** | II | OC | Olaparib 200 mg twice daily | PLD | 32 | 58.5 (45–77) | NA | 6.5 | 3 |
| | | | Olaparib 400 mg twice daily | PLD | 32 | 53.5 (35–76) | NA | 8.8 | |
| **Bang et al[17]** | II | GC | Olaparib 100 mg twice daily plus paclitaxel | Placebo/ paclitaxel | 124 | 63.0 (31–77) | 13.1 | 3.9 | 5 |
| **Ledermann et al[18]** | II | OC | Olaparib 400 mg twice daily | Placebo | 265 | 58.0 (21–89) | 29.7 | 8.4 | 5 |
| **Bang et al[8]** | III | GC | Olaparib 100 mg twice daily plus paclitaxel | Placebo plus paclitaxel | 525 | 58.0 (49–67) | 8.8 | 3.7 | 5 |
| **Pujade-Lauraine et al[7]** | III | OC | Olaparib 300 mg twice daily | Placebo | 295 | 56.0 (51–63) | NA | 19.1 | 5 |
| **Robson et al[9]** | III | BC | Olaparib 300 mg twice daily | Single-agent chemotherapy | 302 | 44.0 (22–76) | 19.3 | 7.0 | 5 |
| **Woll et al[21]** | II | SCLC | Olaparib 300 mg twice daily | Placebo | 220 | 64.0 (42–89) | 9.9 | 3.6 | 4 |
| | | | Olaparib 200 mg three times daily | Placebo | | | 9.0 | 3.6 | |

**Abbreviations:** OC, ovarian cancer; SCLC, small-cell lung cancer; BC, breast cancer; GC, gastric cancer; PLD, PEGylated liposomal doxorubicin; PC, paclitaxel–carboplatin; PFS, progression-free survival; OS, overall survival; NR, not reported.

Qualität der Studien:

- Jaded Score ≥ 3

Studienergebnisse:

PFS

- We found olaparib treatment significantly improved PFS in ovarian cancer (HR 0.44, 95% CI 0.30–0.67; P<0.001)

OS

- Subgroup analysis by tumor type showed that olaparib not significantly improved OS in ovarian cancer (HR 0.83, 95% CI 0.68–1.02; P=0.075

Adverse events

Table 3 Incidence and relative risk of grade 3/4 adverse events comparing olaparib containing therapy vs control

| | Studies | Olaparib-containing therapy | Control | Incidence (95% CI) | RR (95% CI) | P |
|---|---|---|---|---|---|---|
| Anemia | 7 | 136 of 1,004 | 38 of 746 | 12.5 (9.2–16.7) | 2.21 (1.53–3.49) | <0.001 |
| Neutropenia | 5 | 176 of 804 | 137 of 586 | 23.1 (10.3–43.9) | 1.02 (0.64–1.61) | 0.938 |
| Thrombocytopenia | 3 | 10 of 538 | 11 of 433 | 2.1 (0.6–7.1) | 0.79 (0.34–1.84) | 0.583 |
| Fatigue | 7 | 45 of 1,004 | 21 of 746 | 4.8 (3.6–6.3) | 1.60 (0.95–2.71) | 0.076 |
| Nausea | 6 | 18 of 943 | 18 of 943 | 2.3 (1.5–3.6) | 1.45 (0.61–3.46) | 0.403 |
| Vomiting | 5 | 16 of 862 | 9 of 609 | 2.2 (1.4–3.5) | 1.31 (0.57–3.02) | 0.530 |
| Diarrhea | 7 | 11 of 1,004 | 11 of 746 | 1.4 (0.8–2.5) | 0.83 (0.36–1.90) | 0.658 |
| Decreased appetite | 2 | 12 of 343 | 3 of 334 | 1.0 (0.3–3.4) | 3.50 (1.08–11.33) | 0.037 |
| AST increased | 2 | 8 of 467 | 6 of 350 | 1.8 (0.9–3.7) | 0.76 (0.22–2.62) | 0.659 |
| ALT increased | 2 | 7 of 467 | 3 of 350 | 1.5 (0.7–3.1) | 1.72 (0.44–6.62) | 0.434 |
| Headache | 4 | 4 of 617 | 3 of 393 | 0.8 (0.3–2.0) | 0.72 (0.19–2.73) | 0.626 |
| Urinary tract infection | 3 | 2 of 521 | 3 of 390 | 0.5 (0.1–1.7) | 0.50 (0.10–2.58) | 0.408 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RR, risk ratio.

7. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274–1284.
18. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382–1392.
19. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and PEGylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 2012;30(4):372–379.
20. Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015;16(1):87–97.

**Anmerkung/Fazit der Autoren**

In conclusion, our meta-analysis demonstrates that olaparib treatment has better treatment response compared with therapy not containing olaparib. The profile of BRCA mutation may allow expansion of the population able to derive clinical benefit from PARP inhibition, and should be further investigated in future trials. Treatment with olaparib is associated with an increased risk of developing severe anemia.

*Kommentare zum Review*

- Darstellung von UE für alle Indikationen (Ovarial- und Nicht-Ovarialkarzinom)

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**Al Hadidi S et al., 2018 [1].**

PARP (Poly(ADP-Ribose) Polymerase) Inhibitors in Platinum-Sensitive Recurrent Ovarian Cancer: A Meta-Analysis of Randomized Controlled Trials

**Fragestellung**

The objective of this study is to further strengthen the evidence on the use of PARP inhibitors for relapsed platinum-sensitive ovarian tumors

**Methodik**

Population:

- patients with platinum-sensitive recurrent ovarian cancer

Intervention:

- PARP inhibitors

Komparator:

- placebo or another drug

Endpunkte:

- Progression-free survival (PFS) and overall survival (OAS)

Recherche/Suchzeitraum:

- Cochrane database, PubMed, Scopus, and clinicaltrials.gov was carried out from inception to July 2017

Qualitätsbewertung der Studien:

- Delphi

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 4 RCTs

Charakteristika der Population:

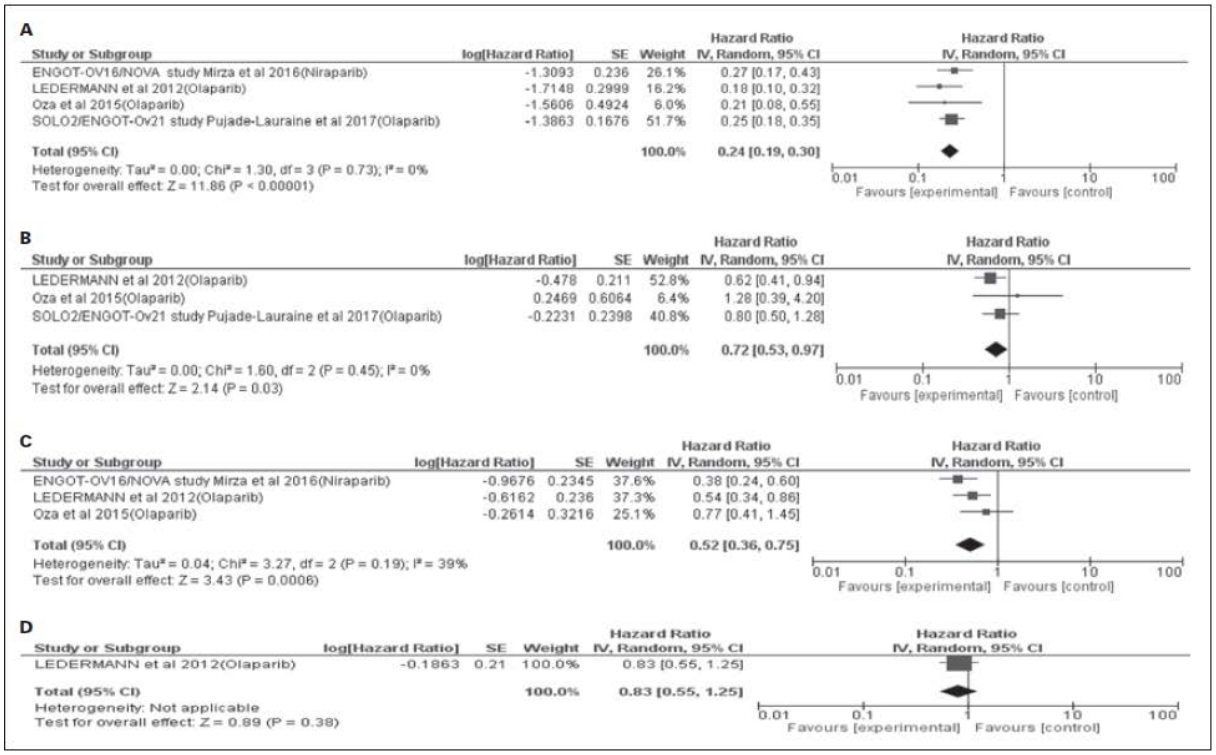
| Study name [ref.] (clinical trials identifier) | Study population | Treatment arms and dosages | Primary endpoint results |
|---|---|---|---|
| Oza et al. 2015 [17] (NCT01081951) | both BRCAm-positive and -negative, platinum-sensitive recurrent HGSOC | arm 1: OLA PO 200 mg BD (days 1–10 of 21-day cycle) along with paclitaxel IV (175 mg/m$^2$ day 1 of 21-day cycle and carboplatin IV (AUC4 day 1 of 21-day cycle). After at least 4 cycles, OLA PO BD continuous for maintenance therapy.<br>arm 2: 6 cycles of paclitaxel IV (175 mg/m$^2$ day 1 of 21-day cycle and carboplatin IV (AUC6 day 1 of 21-day cycle). No maintenance therapy. | PFS<br>arm 1: median 12.2 months<br>arm 2: median 9.6 months<br>p = 0.0012 |
| Ledermann et al. 2012 [18] (NCT00753545) | both BRCAm-positive and -negative, platinum-sensitive recurrent HGSOC | arm 1: OLA PO 400 mg BD (maintenance therapy no later than 8 weeks after platinum-based chemotherapy) until disease progression.<br>arm 2: Placebo. | PFS<br>arm 1: median 8.4 months<br>arm 2: median 4.8 months<br>p < 0.001 |
| ENGOT-OV16/NOVA study Mirza et al. 2016 [16] (niraparib) (NCT01847274) | both BRCAm-positive and -negative, platinum-sensitive HGSOC | arm 1: Niraparib PO 300 mg once daily in 28-day cycle (maintenance therapy no later than 8 weeks after platinum-based chemotherapy) until disease progression.<br>arm 2: Placebo. | PFS<br>Germline mutation cohort<br>arm 1: median 21 months<br>arm 2: median 5.5 months<br>p < 0.001<br><br>Non-germline mutation cohort<br>arm 1: median 9.3 months<br>arm 2: median 3.9 months<br>p < 0.001 |
| SOLO2/ENGOT-Ov21 study Pujade-Lauraine et al. 2017 (olaparip) [21] (NCT01874353) | BRCAm-positive only, platinum-sensitive HGSOC or endometroid | arm 1: OLA PO 300 mg BD (maintenance therapy no later than 8 weeks after platinum-based chemotherapy) until disease progression.<br>arm 2: Placebo. | PFS<br>arm 1: median 19.1 months<br>arm 2: median 5.5 months<br>p < 0.0001 |

AUC = Area under curve; BD = twice daily; BRCAm = germline BRCA mutation carrier; HGSOC = high-grade serous ovarian cancer; OLA = olaparib; PFS = progression-free survival; PO = per os; IV = intravenous.

Qualität der Studien:

| Final Delphi list | ENGOT-OV16/ NOVA study Mirza et al. 2016 [16] (niraparib) | Ledermann et al. 2012 [18] (olaparib) | SOLO2/ENGOT-Ov21 study Pujade-Lauraine et al. 2017 [21] (olaparip) | Oza et al. 2015 [17] (olaparib) |
|---|---|---|---|---|
| Treatment allocation. | yes | yes | yes | yes |
| a. Was a method of randomization performed? | yes | yes | yes | yes |
| b. Was the treatment allocation concealed? | | | | |
| Were the groups similar at baseline regarding the most important prognostic indicators? | yes | yes | yes | yes |
| Were the eligibility criteria specified? | yes | yes | yes | yes |
| Was the outcome assessor blinded? | yes | yes | yes | yes |
| Was the care provider blinded? | yes | yes | yes | no |
| Was the patient blinded? | yes | yes | yes | no |
| Were point estimates and measures of variability presented for the primary outcome measures? | yes | yes | yes | yes |
| Did the analysis include an intention to treat? | yes | yes | yes | yes |

Studienergebnisse:




Forrest plots: A progression-free survival (BRCA-positive), B overall survival (BRCA-positive), C progression-free survival (BRCA-negative), D overall survival (BRCA-negative).

Side Effect Profile

- The most common toxicity noted was grade 1 and 2 nausea. Fatigue was most commonly noted to require dose adjustments. Significant grade 3 and 4 side effects were mainly

hematologic, the most common being anemia, thrombocytopenia, and neutropenia requiring dose interruptions.

- Neutropenia (any grade) was higher in the PARP group; however, it did not reach statistical significance (21.3 vs. 5.6%; p = 0.006). However, we found significantly higher grade 3 or 4 neutropenia in the PARP group (11.7 vs. 1.7%; p = 0.04).

16 Mirza MR, Monk BJ, Herrstedt J, et al.: Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016; 375: 2154–2164.
17 Oza AM, Cibula D, Benzaquen AO, et al.: Olaparib combined with chemotherapy for recurrent platinumsensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol 2015; 16: 87–97.
18 Ledermann J, Harter P, Gourley C, et al.: Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomize phase 2 trial. Lancet Oncol 2014; 15: 852–861.
21 Pujade-Lauraine E, Ledermann JA, Selle F, et al.: Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double- blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18: 1274–1284.

**Anmerkung/Fazit der Autoren**

PARP inhibitors in addition to standard platinum-based regimens along with subsequent maintenance therapy significantly improve PFS and OAS with an acceptable side effect profile in BRCA-positive women with recurrent and previously platinum-sensitive HGSOC.

*Kommentare zum Review*

Einschluss von z.T. nicht zugelassenen AM (Niraparib).

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**Wang H et al., 2018 [17] + Wu S et al., 2017 [18] + Li X et al., 2016 [9] + Staropoli N et al., 2016 [14] + Yi S et al., 2017 [19].**

Angiogenesis Inhibitors for the Treatment of Ovarian Cancer: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

**Fragestellung**

We thus did a systematic review and meta-analysis of randomized controlled trials to reassess the efficacy and safety of angiogenesis inhibitors combined with chemotherapy for ovarian cancer

**Methodik**

Population:

- women with histologically proven epithelial ovarian cancer of any stage (age, ≥ 18 years)

Intervention:

- angiogenesis inhibitors plus conventional chemotherapy

Komparator:

- conventional chemotherapy alone, or angiogenesis inhibitors to no further treatment

Endpunkte:

- OS, PFS, and incidence of adverse events

Recherche/Suchzeitraum:

- 1994 to March 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool was used to assess the risk of bias in included RCTs

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 15 Studies (n=8721), 3 studies platinum-sensitive

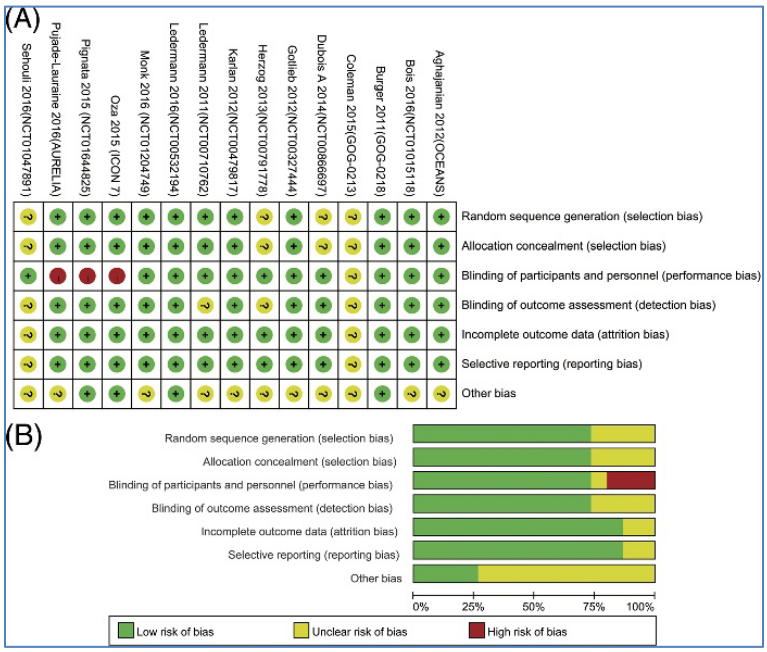
Charakteristika der Population:

| References | Arms | Size | Patients Enrolled | Primary Endpoint | Median (mo) | HR | HR, 95%CI | Median (mo) | HR | HR, 95%CI |
|---|---|---|---|---|---|---|---|---|---|---|
| Burger et al, 2011 (GOG-0218)[3] | TC + PL | 625 | Newly diagnosed | PFS | 10.3 | 0.717 | 0.625–0.824 | 39.3 | 0.885 | 0.750–1.040 |
| | TC + Bev + Bev(m) | 623 | | | 14.1 | | | 39.7 | | |
| Aghajaniann et al, 2012 (OCEANS)[21] | GC + PL + PL(m) | 242 | Platinum-sensitive recurrent | PFS | 8.4 | 0.484 | 0.388–0.605 | 32.9 | 0.952 | 0.771–1.176 |
| | GC + Bev + Bev(m) | 242 | | | 12.4 | | | 33.6 | | |
| Oza et al, 2015 (ICON 7)[22] | TC | 764 | Newly diagnosed | PFS | 17.5 | 0.93 | 0.83–1.05 | 58.6 | 0.99 | 0.85–1.14 |
| | TC + Bev + Bev(m) | 764 | | | 19.9 | | | 58 | | |
| Pujade-Lauraine et al, 2014 (AURELIA)[23] | PLD/PAC/TOP | 182 | Platinum-resistant recurrent | PFS | 3.4 | 0.48 | 0.380–0.600 | 13.3 | 0.85 | 0.66–1.080 |
| | PLD/PAC/TOP + Bev | 179 | | | 6.7 | | | 16.6 | | |
| Coleman et al, 2015 (GOG-0213)[16] | TC | 374 | Platinum-sensitive recurrent | OS | 10.4 | 0.614 | 0.522–0.722 | 37.3 | 0.827 | 0.683–1.005 |
| | TC + Bev + Bev(m) | 374 | | | 13.8 | | | 42.2 | | |

| References | Arms | Size | Patients Enrolled | Primary Endpoint | PFS Median (mo) | PFS HR | PFS HR, 95%CI | OS Median (mo) | OS HR | OS HR, 95%CI |
|---|---|---|---|---|---|---|---|---|---|---|
| Ledermann et al, 2016 (ICON 6)[30] | TC/GC/C + PL | 118 | Platinum-sensitive relapsed | PFS | 8.7 | 0.56 | 0.44–0.72 | 21 | 0.77 | 0.55–1.07 |
| | TC/GC/C + Cediranib + cediranib(m) | 164 | | | 11 | | | 26.3 | | |
| Gotlieb et al, 2012[15] | Aflibercept | 29 | Platinum-resistant relapsed | Time to repeat paracentesis | 6.3 | NA | NA | 16 | 1.023 | 0.562–1.863 |
| | PL | 26 | | | 7.3 | | | 12.9 | | |

Bev, Bevacizumab; C, Carboplatin; GC, Gemcitabine + Carboplatin; m, maintenance therapy; NA, not available; PAC, weekly paclitaxel; PL, placebo; PLD, pegylated liposomal doxorubicin; TC, Paclitaxel + Carboplatin; TOP, topotecan.

Qualität der Studien:



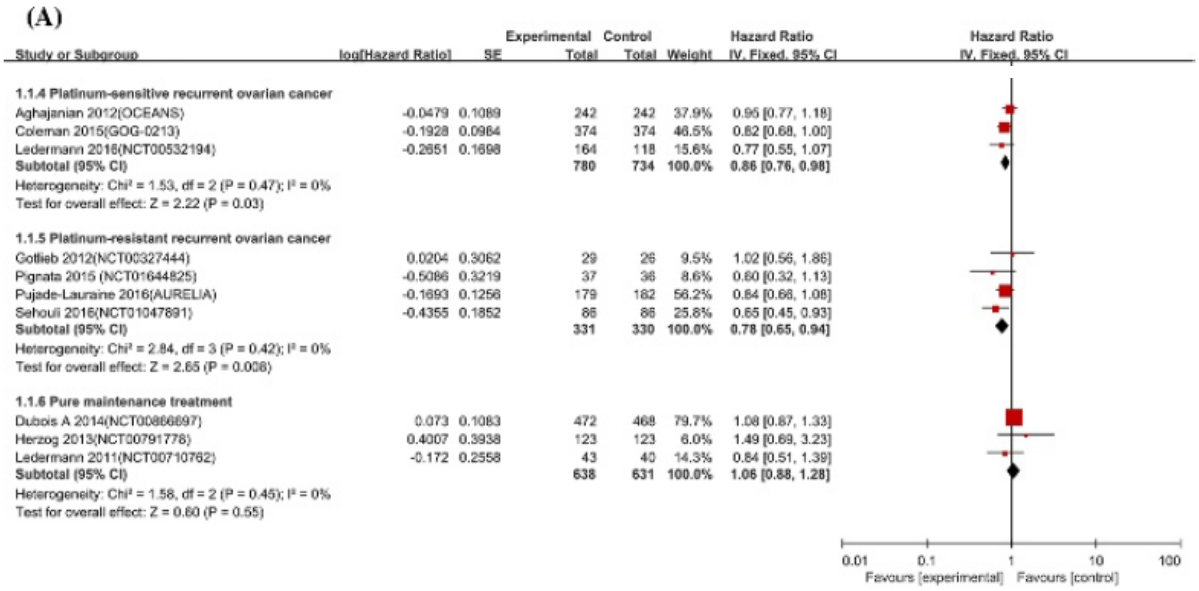

The risk of bias was unclear in the 2 studies that were published in an abstract form. Other RCTs reported sufficient information for randomization excluding 2 trials for which ''Randomize'' was used in abstract and text, but further details were not reported, and none was stopped early. Moreover, 3 studies lacked blinding to participants and personnel, the other 2

trials did not specify whether data collectors and outcome assessors were masked to treatment allocation, and only were not funded by industry.

**Studienergebnisse:**

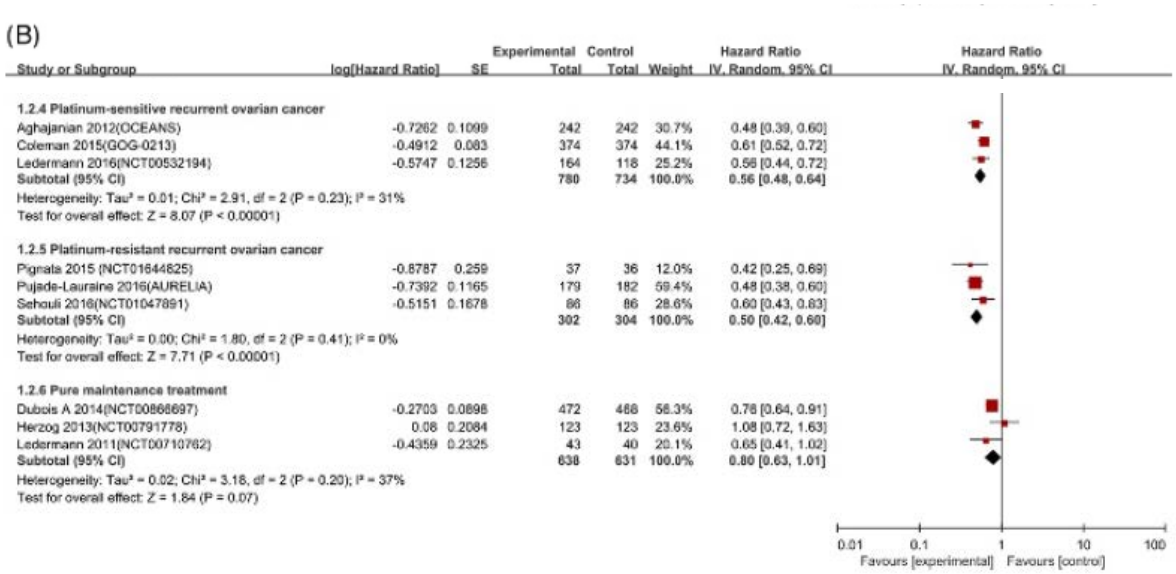
Overall Survival

- Angiogenesis inhibitors had significant survival benefits for both platinum-sensitive recurrent ovarian cancer from 3 trials with a total of 1514 participants (HR, 0.86; 95% CI, 0.76;0.98; I2 = 0%)




Progression-Free Survival

- Moreover, further subgroup analysis comparing the benefit on PFS for platinumsensitive recurrent ovarian cancer (HR, 0.56; 95% CI, 0.48-0.64; I2 = 31%) suggested significantly lower risks of disease progression.




16. Coleman RL, Brady MF, Herzog TJ, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-

sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Gynecol Oncol. 2015;137:3Y4.
21. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol.
30. Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;387:1066Y1074

**Anmerkung/Fazit der Autoren**

Together, although there are significant differences of increased risks of adverse events with antiangiogenics therapy, findings from our meta-analysis are relatively promising. Our findings clearly lend support to the use of angiogenesis inhibitors in combination with chemotherapy in the clinical management of patients with newly diagnosed (especially for high-risk patients) or recurrent ovarian cancer. However, no statistically significant clinical benefit was identified in the pure maintenance settings.

## 2.4 Leitlinien

**Leitlinienprogramm Onkologie, 2020 [7,8].**

*DGGG, DKG, Deutsche Krebshilfe, AWMF*

S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren, Version 4.0 – März 2020, AWMF-Registernummer: 032-035OL

**Aim/Fragestellung:**

Die Leitlinie „Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren“ ist ein evidenz- und konsensusbasiertes Instrument zur Versorgung der Patientinnen mit Borderlinetumoren und bösartigen Tumoren der Eierstöcke, der Tuben und des Peritoneums einschließlich der Keimstrang-Stroma- und Keimzelltumoren.

**Methodik**

Grundlage der Leitlinie

- Interdisziplinäre LL-Entwicklungsgruppe
- Interessenskonflikte dargelegt und Umgang beschrieben
- Strukturierte Konsensfindung
- Gültigkeit der Leitlinie: „living guideline“ Aktualisierung einmal jährlich

Recherche/Suchzeitraum:

- Recherche für Version 4.0.: 01.01.2018-18.03.2019, vorwiegend nach RCT in PubMed

Änderungen bzw. Neuerungen in der Version 4.0.

- Neue Studienergebnisse führten in den Bereichen genetische Beratung, operative Therapie (siehe Lymphonodektomie), Einsatz von PARP-Inhibitoren in der First-Line und der Strahlentherapie zu modifizierten oder neuen Empfehlungen.

LoE nach SIGN

| Grad | Beschreibung |
|---|---|
| **1++** | Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias) |
| **1+** | Gut durchgeführte Metaanalysen, systematische Übersichten von RCTs oder RCTs mit geringem Risiko systematischer Fehler (Bias) |
| **1-** | Metaanalysen, systematische Übersichten von RCTs oder RCTs mit hohem Risiko systematischer Fehler (Bias) |
| **2++** | Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder<br>Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist |
| **2+** | Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist |
| **2-** | Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist |
| **3** | Nicht analytische Studien, z. B. Fallberichte, Fallserien |

| | |
|---|---|
| **4** | Expertenmeinung |

GoR

| Empfehlungsgrad | Beschreibung | Ausdrucksweise |
|---|---|---|
| **A** | Starke Empfehlung | soll |
| **B** | Empfehlung | sollte |
| **0** | Empfehlung offen | kann |

## Empfehlungen

## Systemische Rezidivtherapie

| 9.6. | Konsensbasierte Empfehlung | geprüft 2019 |
|---|---|---|
| EK | Patientinnen mit platinsensitivem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine platinhaltige Kombinationstherapie erhalten. Folgende Kombinationen können in Betracht gezogen werden*:<br>• Carboplatin/Gemcitabin<br>• Carboplatin/Gemcitabin/Bevacizumab**<br>• Carboplatin/Paclitaxel<br>• Carboplatin/Paclitaxel/Bevacizumab**<br>• Carboplatin/pegyliertes liposomales Doxorubicin***<br>i Reihenfolge alphabetisch<br>ii bei Patientinnen mit erstem Rezidiv und ohne vorherige VEGF gerichtete Therapie<br>iii Zulassungsüberschreitend | |

Durch die Addition von Bevacizumab zu einer Chemotherapie bestehend aus Carboplatin/Gemcitabin oder Carboplatin/Paclitaxel konnte das progressionsfreie Überleben und die Ansprechrate gegenüber der alleinigen Chemotherapie deutlich verbessert werden [481, 482]. Daten zur Lebensqualität liegen in diesen Studien jedoch nicht vor (Stand 8/18: Addition von Bevacizumab nur zugelassen bei Patientinnen mit erstem Rezidiv und ohne vorherige VEGF gerichtete Therapie). Die 3 im Nachfolgenden genannten Chemotherapiekombinationen hatten allesamt im Rahmen von prospektiv randomisierten Phase-III-Studien im Vergleich zum jeweils gültigen Standardregime einen positiven Effekt gezeigt. Bei der Therapie des platinsensitiven Ovarialkarzinoms konnten die Kombinationen aus Carboplatin/Paclitaxel [459] und Carboplatin/Gemcitabin [483] einen Vorteil im progressionsfreien Überleben, bzw. Carboplatin/Paclitaxel auch im Gesamtüberleben im Vergleich zu einer Platinmonotherapie bzw. Kombination aus Platin/Doxorubicin/Cyclophosphamid nachweisen. Carboplatin/pegyliertes liposomales Doxorubicin zeigte einen Vorteil im progressionsfreien Überleben im Vergleich zu Carboplatin/Paclitaxel [484].

Aktuell liegen Daten zu einer weiteren Kombinationstherapie vor. Die Kombination von Carboplatin/Paclitaxel/Bevacizumab konnte in der GOG 213 gegenüber der Standardchemotherapie eine Verbesserung auch des Gesamtüberlebens belegen.

Eine weitere randomisierte Phase III Studie von Carboplatin in Kombination mit Topotecan im Vergleich zu anderen platinbasierten Kombinationstherapien (ohne Bevacizumab) konnte keine Überlegenheit bezüglich des primären Endpunktes 12 Monats-PFS zeigen [485]

Des Weiteren konnte ein Vorteil im progressionsfreien und Gesamtüberleben bei Patientinnen, die mit der Kombination aus Trabectedin und pegyliertem liposomalem Doxorubicin behandelt wurden, im Vergleich zu einer Monotherapie aus pegyliertem liposomalem Doxorubicin beobachtet werden; wobei dieser Effekt nur in der Subgruppe der partiell platinsensitiven Rezidive beobachtet wurde [486]. In dieser Subgruppe konnte bisher allerdings keine Überlegenheit einer Nicht-Platinhaltigen Therapie (pegyliertes liposomales Doxorubicin) im Vergleich zu einer platinhaltigen Therapie aufgezeigt werden [487]. Somit ist auch in dieser Subpopulation der Standard eine platinbasierte Therapie. Der direkte Vergleich zwischen platinbasierter Kombination versus Trabectedin mit peglyliertem liposomalen Doxorubicin wurde in der Inovatyon-Studie untersucht. Die Ergebnisse sind noch ausstehend.

459. Parmar, M.K., et al., Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet, 2003. 361(9375): p. 2099-106. https://www.ncbi.nlm.nih.gov/pubmed/12826431
481. Aghajanian, C., et al., OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol, 2012. 30(17): p. 2039-45. https://www.ncbi.nlm.nih.gov/pubmed/22529265
482. Aghajanian, C., et al., Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol, 2015. 139(1): p. 10-6. https://www.ncbi.nlm.nih.gov/pubmed/26271155
483. Pfisterer, J., et al., Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol, 2006. 24(29): p. 4699-707. https://www.ncbi.nlm.nih.gov/pubmed/16966687

484. Pujade-Lauraine, E., et al., Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol, 2010. 28(20): p. 3323-9. https://www.ncbi.nlm.nih.gov/pubmed/20498395
485. Sehouli, J., et al., Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or pegylated liposomal doxorubicin plus carboplatin (PLDC): a randomized phase III trial of the NOGGO-AGO-Study Group-AGO Austria and GEICO-ENGOT-GCIG intergroup study (HECTOR). Ann Oncol, 2016. 27(12): p. 2236-2241. https://www.ncbi.nlm.nih.gov/pubmed/27789470
486. Monk, B.J., et al., Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. J Clin Oncol, 2010. 28(19): p. 3107-14. https://www.ncbi.nlm.nih.gov/pubmed/20516432
487. Pignata, S., et al., Randomized Controlled Trial Testing the Efficacy of Platinum-Free Interval Prolongation in Advanced Ovarian Cancer: The MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study. J Clin Oncol, 2017. 35(29): p. 3347-3353. https://www.ncbi.nlm.nih.gov/pubmed/28825853

| 9.9. | Evidenzbasierte Empfehlung | geprüft 2019 |
|---|---|---|
| Empfehlungsgrad<br>B | Bei Patientinnen mit Rezidiv eines high-grade Ovarialkarzinoms nach Ansprechen auf eine platinhaltige Rezidivherapie sollte eine Erhaltungstherapie mit einem PARP-Inhibitor angeboten werden. | |
| Level of Evidence<br>1+ | Primärstudien: [495-502] | |

| 9.10. | Evidenzbasierte Empfehlung | geprüft 2019 |
|---|---|---|
| Empfehlungsgrad<br>0 | Bei Patientinnen mit platin-sensitivem Rezidiv eines BRCA-mutierten high-grade Ovarialkarzinoms mit 2 oder mehr platinhaltige Vortherapien, die nicht mehr für eine platinhaltige Rezidivtherapie geeignet sind, kann eine Mono-Therapie mit einem PARP-Inhibitor* angeboten werden.<br><br>*Zugelassen ist Rucaparib (Stand 9/2018) | |
| Level of Evidence<br>2+ | Primärstudien: [495-502] | |

Olaparib

Die Effektivität von Olaparib als Erhaltungstherapie wurde in der Studie 19 überprüft [495-497] [505]. Hier wurden Patientinnen mit einen high-grade serösen Rezidiv in einer randomisierten, doppelblinden, placebokontrollierten Studie eingeschlossen, die zwei oder mehr platinhaltige Vortherapien erhalten hatten und eine Partial- oder Komplett-Remission nach der letzten platinhaltigen Therapie erreicht hatten. Die Patientinnen wurden 1:1 randomisiert und erhielten bis zum Erkrankungsprogress entweder Olaparib (Kapseln, insgesamt 400mg zweimal täglich) oder Placebo. Der primäre Endpunkt war das progressionsfreie Überleben (PFS), welches bei Patientinnen unter Olaparib-Therapie im Vergleich zu Patientinnen im Placeboarm signifikant länger war (PFS median 8,4 Monate vs. 4,8 Monate; HR 0,35; 95% CI, 0,25-0,49; P<0,001) [495]. Bei 51,3 % der Patientinnen zeigte sich eine deletären BRCA 1/2 Mutation in der Keimbahn und/ oder im Tumor. Für die retrospektiv definierte Subgruppe mit einer BRCA1/2 Mutation zeigte sich ein noch größerer Nutzen durch eine Erhaltungstherapie (PFS median 11,2 Monate vs. 4,3 Monate; HR 0,18; 95% CI 0,11-0,31; P<0,00001). Darüberhinaus war in der retrospektiv definierte Subgruppe nicht-BRCA mutierten Patientinnen einen PFS-Vorteil gezeigt worden (PFS median 7,4 Monate vs. 5,5 Monate; HR=0,54; CI 0,34-0,85). Schwere Nebenwirkungen traten unter Olaparib bei 18 % der Patienten (vs. 9 % unter Plazebo) auf. Die häufigsten schweren Nebenwirkungen (> Grad 3) unter Olaparib waren Fatigue (7 % vs. 3 %) und Anämie (5 % vs. <1 %) [495]. Für das Gesamtüberleben zeigte sich kein signifikanter Unterschied [497].

Aufgrund der retrospektiv durchgeführten Subgruppenanalyse wurde die Studie 19 für die Population der Frauen mit BRCA1/2 Mutation mit einem LoE von 2+ bewertet. Wegen der fehlenden Belege für einen Überlebensvorteil, wurde eine abgeschwächte Empfehlung (Empfehlungsgrad B) abgegeben.

Die Daten der Phase-3-Studie SOLO2 (NCT01874353) mit Olaparib 600mg täglich als Erhaltungstherapie bei Patientinnen mit high-grade serösen und endometrioidem platinsensiblen Ovarialkarzinom bei mindestens partiellen Ansprechen auf die aktuelle platinhaltige Therapie und einer BRCA1/2 Mutation bestätigten die Effektivität des Medikaments (PFS median

19,1 Monate vs. 5,5 Monate, HR 0,30, 95% CI 0,22-0,41) [501, 506]. In der Studie wurde bei ähnlichen Nebenwirkungsprofil die Darreichung in Tabletten-Form (2x2 Tabletten, insgesamt 600mg) geändert. Somit soll diese Form präferiert werden.

Olaparib ist aufgrund einer nicht randomisierten Studie an 298 Patientinnen mit BRCA-Mutationen für die vierte und fünfte Therapielinie als Monotherapie in den USA zugelassen, eine Zulassung für Europa liegt aktuell nicht vor.

Da bei keiner der Patientinnen in dieser Studie eine zusätzliche Gabe von Bevacizumab erfolgte, gibt es keine Daten zu einer gleichzeitigen Erhaltungstherapie mit Olaparib und Bevacizumab [495, 496, 498].

Rucaparib

Die aktuelle Zulassung in der EU basiert auf zwei multizentrische, einarmige Studien – Studie 10 (NCT01482715) und ARIEL2 (NCT01891344) – mit Frauen mit fortgeschrittenem BRCA-mutierten Eierstockkrebs, die nach zwei oder mehr vorherigen Chemotherapien fortgeschritten waren.

Alle Patientinnen erhielten Rucaparib in einer Dosis von 600 mg zweimal täglich als Monotherapie. Die Behandlung wurde bis zur Progression der Erkrankung oder bis zur inakzeptablen Toxizität fortgesetzt. Der primäre Studienendpunkte war die objektive Ansprechrate (ORR), die vom Prüfer nach den Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 bewertet wurde.

Basierend auf der Beurteilung des Ansprechens durch den Prüfer zeigte Rucaparib eine objektive Ansprechrate (ORR) von 54,7 % (N=106) in der eher platin-resistenten und 64,6 % in der platinsensitiven Population (n=79). Eine kombinierte Analyse mehrerer Studien zu Rucaparib zeigte bei Monotherapie mit Rucaparib 600 mg bei Patientinnen mit einer BRCA-Mutation ein medianes PFS von 10 Monaten [499]. Darüber hinaus wurde im Rahmen der doppelblinden Phase-3-Studie ARIEL3 (NCT01968213) – unabhängig vom BRCA-Status – eine deutliche Verlängerung des PFS bei PARPi-naiven Patientinnen mit platinsensiblen high-grade serösen und endometrioidem Rezidiv des Ovarialkarzinoms, die eine Erhaltungstherapie mit Rucaparib 600mg täglich nach mindestens partiellem Ansprechen auf die aktuelle platinhaltige Therapie erhalten haben, beobachtet [502]. In der Studie wurden 564 Patientinnen mit einem guten bis leicht eingeschränkten Allgemeinzustand (ECOG 0-1) im Verhältnis 2:1 entweder zu Rucaparib oder Plazebo randomisiert. Das mediane PFS -der primäre Endpunkt der Studie - betrug in der ITT-Population 10,8 Monate unter Rucaparib (95% KI 8,3-11-4) versus 5,4 Monate unter Plazebo (95% KI 5,3-5,5; HR 0.36 [0,30-0,45] p<0.0001). Bei Patientinnen mit BRCA-Mutation betrug der Unterschied 16,6 Monate (95% KI 13,4-22,9); versus 5,4 Monate (95% KI 3,4-6,7, HR 0.23 [95% KI 0,16-0,34]; p<0.0001) und bei Patientinnen mit Rekombinationsdefekten 13,6 Monate (95 KI 10,9-16,2) versus 5,4 Monate (95 % KI 5,1-5,6; HR 0.32 [0.24-0.42]; p<0.0001).

Unterschiede bzgl. des Gesamtüberlebens zeigten sich zum Zeitpunkt des Datenschnitts (04/2017) nicht (22 % Verstorbene in der Rucaparib-Gruppe versus 22 % in der Plazebo-Gruppe). Eine Auswertung bzgl. des Gesamtüberlebens ist geplant, wenn 70 % der Patientinnen verstorben ist. Nachteile zeigten sich unter der Rucaparib-Therapie bzgl. der Symptomatik (erfasst über die DRS-P Subskala des FOSI-18) und hinsichtlich von schweren unerwünschten Ereignissen (CTCAE-Grad ≥ 3) (56 % vs. 15 %) [502].

495. Ledermann, J., et al., Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med, 2012. 366(15): p. 1382-92. https://www.ncbi.nlm.nih.gov/pubmed/22452356
496. Ledermann, J., et al., Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol, 2014. 15(8): p. 852-61. https://www.ncbi.nlm.nih.gov/pubmed/24882434
497. Ledermann, J.A., et al., Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol, 2016. 17(11): p. 1579-1589. https://www.ncbi.nlm.nih.gov/pubmed/27617661
498. Oza, A.M., et al., Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol, 2015. 16(1): p. 87-97. https://www.ncbi.nlm.nih.gov/pubmed/25481791
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500. Mirza, M.R., et al., Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med, 2016. 375(22): p. 2154-2164. https://www.ncbi.nlm.nih.gov/pubmed/27717299
501. Pujade-Lauraine, E., et al., Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol, 2017. 18(9): p. 1274-1284. https://www.ncbi.nlm.nih.gov/pubmed/28754483
502. Coleman, R.L., et al., Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet, 2017. 390(

**Francis J et al., 2017 [2].**

*Cancer Care Ontario Guideline 4-3 Version 4*

Systemic Therapy for Recurrent Epithelial Ovarian Cancer

**Fragestellung:**

To recommend systemic therapy options for women with recurrent epithelial ovarian cancer including fallopian tube and primary peritoneal cancers.

**Methodik**

Grundlage der Leitlinie:

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- In the prior 2011 guideline by the same authors, the literature search was current as of 2011
- MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from April 1, 2011 to May 30, 2017 for systematic reviews and primary studies.

LoE

- Cochrane risk of bias tool and GRADE

GoR

- • Empfehlungsstärken über die Formulierung abgebildet

**Empfehlungen**

| *Recommendation 1* |
|---|
| Systemic therapy for recurrent ovarian cancer is not curative. As such, it is recognized that, to determine the optimal therapy, each patient needs to be assessed individually in terms of recurrence, sensitivity to platinum, toxicity, ease of administration, and patient preference. |

| *Recommendation 2* |
|---|
| All patients should be offered the opportunity to participate in clinical trials, if appropriate. |

| *Recommendation 3* |
|---|
| Chemotherapy for patients with platinum-sensitive recurrent ovarian cancer:<br>• If the option to participate in a clinical trial is not available, combination platinum-based chemotherapy should be considered, providing that there are no contra-indications. The decision regarding which combination to use should be based on toxicity experienced with primary therapy, patient preference, and other factors. Recommended combinations are:<br>○ carboplatin and paclitaxel (C-P)<br>○ carboplatin and gemcitabine<br>○ carboplatin and pegylated liposomal doxorubicin (C-PLD)<br>• If combination platinum-based chemotherapy is contraindicated, then a single platinum agent should be considered. Carboplatin has demonstrated efficacy across trials and has a manageable toxicity profile.<br>• If a single platinum agent is not being considered (e.g., because of toxicity or allergy), |

then monotherapy with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a reasonable treatment option.

***Key Evidence for Recommendation 3***

- A 976-patient study, CALYPSO [2], compared C-P with C-PLD and found an improvement in progression-free survival (PFS) with the C-PLD combination (11.4 vs. 9.3 months; p=0.005), a more favourable toxicity profile, no difference in overall survival (OS) (although significantly more patients crossed over to the C-PLD arm), and a superior crossover treatment rate in the C-P arm. Global quality of life (QOL) scores did not differ between groups [3].
- A 672-patient study, OVA-301 [4], compared PLD with trabectedin-PLD, and found a statistically significantly improved PFS with the combination (7.3 vs. 5.8 months; p=0.019). Despite this finding, which implies the viability of the combination as a treatment option, the trabectedin-PLD combination is not recommended at this time, based on the finding of no differences in QOL [5] or OS [6], the lack of clinical significance of a six-week PFS difference, the lack of comparison with the Gynecologic Cancer InterGroup standard taxane and platinum agent [7], and the elevated rate of adverse events such as raised liver enzymes, non-fatal congestive heart failure, and neutropenia in the combination group.
- A study by Sehouli et al. [8] of topotecan versus topotecan combined with other agents did not find a benefit with the combination therapy in a population of mainly platinum-sensitive women; thus, topotecan combination therapy is not recommended.
- Two smaller trials that compared PLD with gemcitabine showed no difference in PFS. A small significant difference in OS was found in one trial (56 weeks for PLD vs. 51 weeks for gemcitabine; p=0.048) [9]. The adverse events profiles differ for these two agents; therefore, gemcitabine can be considered another option in this patient population, considering patient preference and previous toxicity [9,10].

***Recommendation 4***

<u>For patients with platinum-sensitive recurrent ovarian cancer:</u>

- Women with platinum-sensitive recurrent ovarian cancer should be offered chemotherapy with biologics after a discussion concerning the safety profile

Targeted agents:

- Bevacizumab combined with combination chemotherapy and as maintenance therapy can be considered.
- Cediranib administered during the chemotherapy and maintenance therapy can be considered.
- PolyADP-ribose polymerase (PARP) inhibitors are recommended for patients with known *BRCA* 1 or 2 mutation (somatic and germline) as maintenance treatment post platinum-based chemotherapy for recurrent disease.
- Niraparib can be considered for patients who are *BRCA* wild-type as maintenance post-platinum-based chemotherapy for recurrent disease.

***Qualifying Statements for Recommendation 4***

- With the increase in evidence supporting the use of PARP inhibitors in patients with homologous recombination deficiency (HRD) mutations, consideration should be given to testing the *BRCA* status of all women with ovarian cancer at initial diagnosis.
- PARP inhibitors have demonstrated an increase in PFS in patients with *BRCA* mutations without a significant improvement in OS.

- Women with wild-type *BRCA* also showed a minor improvement in PFS.

***Key Evidence for Recommendation 4***

- It was shown that in the platinum-sensitive population of the OCEANS phase III randomized controlled trial (RCT), PFS for bevacizumab with gemcitabine and carboplatin (BEV+CT) was superior compared with carboplatin with gemcitabine plus placebo (CT) (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.39 to 0.61). Median PFS of 12.4 months in the BEV+CT arm versus 8.4 months in the CT arm [11].
- It was shown that in the platinum-sensitive population of the moderate quality ICON6 phase III RCT, PFS for Arm C with cediranib was superior compared with the reference Arm A of platinum-based therapy plus placebo (HR, 0.56; 95% CI, 0.44 to 0.72). Median PFS was 11.0 months in the experimental arm versus 8.7 months in the non-experimental arm [12].
- Niraparib significantly prolonged PFS in platinum-sensitive patients when compared with a placebo, in patients with no germline *BRCA* mutations (HR, 0.45; 95% CI, 0.34 to 0.61; p<0.001) [13].

***Interpretation of Evidence for Recommendation 4***

- The above listed recommendations are conditional in nature (i.e., "can be considered") considering the trade-off between the benefits (i.e., PFS) weighed against the harms (i.e., adverse effects).
- Based on moderate quality of evidence in the OCEANS trial [11,14], statistically significantly increased risks for BEV+CT vs. CT were shown for the following adverse events:
  - Serious adverse events (grade 3 to 5): relative risks [RR], 1.53; 95% CI, 1.11 to 2.09
  - Grade ≥3 hypertension: RR, 21.22; 95% CI, 5.21 to 86.51
  - Grade ≥3 proteinuria: RR, 12.73; 95% CI, 3.06 to 52.96
  - Notably, very wide confidence intervals were shown for both grade ≥3 hypertension and proteinuria due to few events in the CT arm (<5 events).
- In the ICON6 trial [12], statistically significantly increased risks during the chemotherapy phase for Arms B+C of platinum-based chemotherapy plus cediranib vs. the reference Arm A of platinum-based chemotherapy plus placebo were shown for the following adverse events:
  - Grade ≥3 fatigue: RR, 2.11; 95% CI, 1.07 to 4.11
  - Grade 3 to 4 diarrhea: RR, 5.94; 95% CI, 1.45 to 24.34
  - Grade 3 to 5 hypertension: RR, 3.32; 95% CI, 1.21 to 9.10
  - Notably, very wide confidence intervals were shown for grade 3 to 5 diarrhea due to few events in the CT arm (<5 events).

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**Scottish Intercollegiate Guidelines Network 2013 [13].**

*Scotland; SIGN 135; A national clinical guideline (November 2013 • **Revised 2018**)*

Management of epithelial ovarian cancer

**Fragestellung:**

This guideline provides recommendations based on current evidence for best practice in the management of epithelial ovarian cancer. It excludes the management of borderline tumours.

**Methodik**

Grundlage der Leitlinie:

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.: Guideline was revised in 2018

Recherche/Suchzeitraum:

- Medline, Embase, Cinahl, PsycINFO and the Cochrane Library: 2003-2012; Update: 2017

Level of Evidence (LoE) / Strength of Recommendation (SoR):

| KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS | |
|---|---|
| **LEVELS OF EVIDENCE** | |
| $1^{++}$ | High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| $1^{+}$ | Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias |
| $1^{-}$ | Meta-analyses, systematic reviews, or RCTs with a high risk of bias |
| $2^{++}$ | High quality systematic reviews of case control or cohort studies<br>High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| $2^{+}$ | Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| $2^{-}$ | Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies, eg case reports, case series |
| 4 | Expert opinion |
| **GRADES OF RECOMMENDATION** | |
| *Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.* | |
| A | At least one meta-analysis, systematic review, or RCT rated as $1^{++}$, and directly applicable to the target population; or<br>A body of evidence consisting principally of studies rated as $1^{+}$, directly applicable to the target population, and demonstrating overall consistency of results |
| B | A body of evidence including studies rated as $2^{++}$, directly applicable to the target population, and demonstrating overall consistency of results; or<br>Extrapolated evidence from studies rated as $1^{++}$ or $1^{+}$ |
| C | A body of evidence including studies rated as $2^{+}$, directly applicable to the target population and demonstrating overall consistency of results; or<br>Extrapolated evidence from studies rated as $2^{++}$ |
| D | Evidence level 3 or 4; or<br>Extrapolated evidence from studies rated as $2^{+}$ |
| **GOOD PRACTICE POINTS** | |
| ✓ | Recommended best practice based on the clinical experience of the guideline development group |

## Empfehlungen

| | | |
|---|---|---|
| **6.3** | **RELAPSED DISEASE** | |
| 6.3.1 | SYSTEMIC THERAPY IN RECURRENT OVARIAN CANCER | |
| | Relapse in ovarian cancer occurs in approximately 75% of patients and is therefore a significant problem, affecting approximately 375 patients a year in Scotland. Relapsed ovarian cancer is incurable but prolonged survival (>1 year) is possible in the majority of patients and improved treatment following relapse has resulted in incremental increases in the overall survival from ovarian cancer. | |
| | Three systematic reviews, one meta-analysis, and 14 good-quality RCTs of chemotherapy for relapsed ovarian cancer support the use of platinum-based combination chemotherapy (where likely to be tolerated) in platinum-sensitive relapsed disease.[158-175] For platinum-resistant ovarian cancer, the evidence is less clear, with data in some cases derived from small patient subgroups in studies of relapsed ovarian cancer rather than studies which were performed specifically in the platinum-resistant setting. | $1^{++}$<br>$1^{+}$ |

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| The results from two systematic reviews including 13 and nine RCTs, respectively, provide good evidence that platinum based combination chemotherapy provides a survival benefit when compared to single agent platinum chemotherapy, although combination therapy was associated with higher rates of adverse events.[158,160] | 1++ |
| In the setting of platinum-sensitive relapsed ovarian cancer there is evidence from a large RCT with a low risk of bias that the combination of carboplatin and pegylated liposomal doxorubicin hydrochloride (PLDH) (CD arm) is more tolerable than carboplatin and paclitaxel (CP arm) and that it confers a progression-free survival benefit (median PFS 11.3 months for CD arm *v* 9.4 months for CP arm; HR=0.823, 95% CI 0.72 to 0.94, p=0.005).[172] | 1++ |
| Trabectedin combined with PLDH improved PFS compared to monotherapy, and increased overall survival compared to topotecan alone. However, this therapy was not as cost effective as paclitaxel or PLDH plus platinum.[220] Monotherapy with PLDH or paclitaxel is cost effective for the treatment of women with platinum-sensitive disease when platinum-based treatment is unsuitable.[220] | 1++ |
| Potential toxicities with combination therapy with either paclitaxel or PLDH include myelosuppression, fatigue, nausea, vomiting and palmoplantar erythrodysasthesiae. Treatment with paclitaxel is also associated with alopecia, neuropathy, and arthralgia. Stomatitis has been reported mainly with use of PLDH.[220] The use of platinum combination therapy compared to single-agent platinum depends on patient comorbidity and willingness to accept the additional toxicity, and the pros and cons of each approach should be discussed with the patient. | 1++ |
| In patients with platinum-resistant ovarian cancer, a network meta-analysis identified no significant difference in PFS or OS benefit between PLDH, three-weekly paclitaxel or topotecan monotherapy. This was in line with the findings from the individual trials.[220] NICE reported that paclitaxel or PLDH as monotherapy were cost effective and concluded that either could be recommended for treatment of women with platinum-resistant or refractory ovarian cancer.[220] | 1++ |

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| A trial of olaparib reported improved PFS of 19.1 months compared to 5.5 months for placebo; HR 0.30 (95% CI 0.22 to 0.41).[224] Twelve-month PFS was 65% in the olaparib group versus 21% placebo, and 43% versus 15% for 24 month survival.[224] Overall survival data at five-year follow up from the Phase II trial showed improved survival compared to placebo, although it was not sufficient to be statistically significant (HR 0.73, 95% CI 0.55 to 0.96 across the patient groups. Median overall survival was 29.8 months with olaparib, compared to 27.8 in the placebo group.[225] | 1++ |
| Rucarapib also showed benefit with a PFS of 10.8 months versus 5.4 months with placebo, HR 0.36, 95% CI 0.30 to 0.45.[222] | 1++ |
| In the trial of niraparib PFS was longest in patients with a germline BRCA mutation (PFS 21 months *v* 5.5 months for placebo, HR 0.27 95% CI 0.17 to 0.41). Overall, for patients in the non-germline *BRCA* mutation cohort PFS was 9.3 months versus 3.9 months for placebo, HR 0.45 (95% CI 0.34 to 0.61). For patients who were non-germline *BRCA* with tumours with homologous recombination deficiency the PFS was 21.9 months versus 3.8 months placebo, HR 0.38, 95% CI 0.24 to 0.59.[223] | 1++ |
| Patients reported quality of life to be similar whether on PARP inhibitor or placebo.[222-224] All three trials reported anaemia as a common serious adverse event.[222-224] Thrombocytopenia and neutropenia were commonly reported with the use of niraparib, but could be managed with dose reduction.[223] The trials of olaparib and rucarapib resulted in the death of one patient due to the development of myeloid leukaemia.[222,224] Another patient in the rucarapib cohort died from treatment-related myelopdysplastic syndrome.[222] In the long-term data from the phase II trial of olaparib, three patients developed myelodysplastic syndromes or acute myeloid leukaemia, one of whom was in the placebo group.[225] | 1++ |
| SMC has accepted olaparib for monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian cancer who are in response to platinum-based chemotherapy. Niraparib is accepted for monotherapy for maintenance treatment of patients with platinum-sensitive relapsed non germline *BRCA* mutation high grade serous epithelial ovarian cancer who are in response to platinum-based chemotherapy *(see section 10.4)*. Niraparib is licensed for this use but SMC advice for the use of niraparib and rucarapib in Scotland is not available. | |

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| A | Olaparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive *BRCA*-mutated ovarian cancer. |
| A | Niraparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive non-germline *BRCA*-mutated ovarian cancer. |

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# 3 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 7 of 12, July 2020) am 01.07.2020**

| # | Suchfrage |
|---|---|
| 1 | MeSH descriptor: [Ovarian Neoplasms] explode all trees |
| 2 | MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees |
| 3 | MeSH descriptor: [Peritoneal Neoplasms] explode all trees |
| 4 | #1 OR #2 OR #3 |
| 5 | (ovar* OR (fallopian NEXT tube) OR tubal OR (primary AND peritone*) OR (serous NEXT surface NEXT papillary)):ti,ab,kw |
| 6 | (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw |
| 7 | #5 AND #6 |
| 8 | #4 OR #7 |
| 9 | #8 with Cochrane Library publication date from Jul 2015 to present, in Cochrane Reviews |

**Systematic Reviews in Medline (PubMed) am 01.07.2020**

| # | Suchfrage |
|---|---|
| 1 | ovarian neoplasms/therapy[mh] OR fallopian tube neoplasms/therapy[mh] OR peritoneal neoplasms/therapy[mh] |
| 2 | ovar*[tiab] OR fallopian tube[tiab] OR tubal[tiab] OR (primary[tiab] AND peritone*[tiab]) OR serous surface papillary[tiab] |
| 3 | (((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab] |
| 4 | ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])) |
| 5 | #2 AND #3 AND #4 |
| 6 | #1 OR #5 |
| 7 | (#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) |

| | |
|---|---|
| | AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))))) |
| 8 | ((#7) AND ("2015/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])) |
| 9 | (#8) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in Medline (PubMed) am 01.07.2020**

| # | **Suchfrage** |
|---|---|
| 1 | ovarian neoplasms[mh] OR fallopian tube neoplasms[mh] OR peritoneal neoplasms[mh] |
| 2 | ovar*[tiab] OR fallopian tube[tiab] OR tubal[tiab] OR (primary[tiab] AND peritone*[tiab]) OR serous surface papillary[tiab] |
| 3 | (((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab] |
| 4 | #2 AND #3 |
| 5 | #1 OR #4 |
| 6 | (#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]) |
| 7 | (#6) AND ("2015/07/01"[PDAT] : "3000"[PDAT]) |
| 8 | (#7) NOT (retracted publication [pt] OR retraction of publication [pt]) |

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**Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6**

**2020-B-179**

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Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden

**Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei "***Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden***"? Wie sieht die Versorgungspraxis in Deutschland aus?**

Zusammenfassung

Die Erkrankungs- und Sterberaten des Ovarialkarzinom sind in Deutschland in den letzten 15 Jahren langsam gesunken, dennoch besteht besonders in den fortgeschrittenen Stadien weiterhin ein großer, ungedeckter medizinischer Bedarf. Der von uns im Folgenden verwendete Begriff „Ovarialkarzinom" umfasst die gesamte Indikation „epitheliales Ovarialkarzinom, Eileiterkarzinom oder primäres Peritonealkarzinom".

- Standard in der systemischen Zweitlinientherapie ist eine erneute Platin-haltige Kombinationstherapie
    - Als zweckmäßige Vergleichstherapie für die anschließende Erhaltungstherapie ist die Therapie mit einem PARP-Inhibitor oder mit Bevacizumab geeignet.

Behandlungsstandard als Basis der vergleichenden Bewertung eines neuen Arzneimittels in der Erhaltungstherapie von Patientinnen mit Rezidiv eines Platin-sensiblen Ovarialkarzinoms, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden, ist die Gabe eines PARP-Inhibitors oder von Bevacizumab.

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Fragestellung

Gefragt wird nach dem Standard in der Erhaltungstherapie bei Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten Chemotherapie in Remission (komplett oder partiell) befinden.

Eine weitere Präzisierung der Fragestellung, z. B. nach Art und Ansprechen vorheriger Erhaltungstherapien, liegt nicht vor.

Stand des Wissens

Pro Jahr erkranken in Deutschland etwa 7.000 - 7.500 Frauen an einem Ovarialkarzinom [1]. Das mittlere Erkrankungsalter liegt bei etwa 70 Jahren. Neben allgemeinen Risiken wie Alter, Übergewicht und hormonellen Faktoren ist die genetische Prädisposition relevant. Die Erkrankungs- und Sterberaten sind in den letzten 15 Jahren zwar langsam gesunken, die 5-Jahres-Überlebensrate liegt aber unter 50%. In den Stadium I und II ist die Therapie kurativ, auch in den Stadien II und IV ist eine Kuration und Langzeitkontrolle erreichbar. Nichtsdestotrotz ist die Rezidiv- und Progressionsgefahr in den fortgeschrittenen Stadien sehr hoch, so dass für diese Patientinnen ein hoher Bedarf an Erhaltungstherapien zur Symptom- und Progressionskontrolle besteht.

Patientinnen mit platinsensitivem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine platinhaltige Kombinationstherapie erhalten. Folgende Kombinationen können in Betracht gezogen werden* [2]:

- Carboplatin/Gemcitabin
- Carboplatin/Gemcitabin/Bevacizumab**
- Carboplatin/Paclitaxel
- Carboplatin/Paclitaxel/Bevacizumab**
- Carboplatin/pegyliertes liposomales Doxorubicin

* Reihenfolge alphabetisch
**bei Patientinnen mit erstem Rezidiv und ohne vorherige VEGF gerichtete Therapie

Durch die Addition von Bevacizumab zu einer Chemotherapie bestehend aus Carboplatin/Gemcitabin oder Carboplatin/Paclitaxel konnte das progressionsfreie Überleben und die Ansprechrate gegenüber der alleinigen Chemotherapie deutlich verbessert werden.

**Kontaktdaten**

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Da die meisten Patientinnen bereits in der First-Line Therapie eine Anti-VEGF erhalten haben besteht die Option einer Erhaltungstherapie mit PARPi.

Patientinnen mit einem high-grade Ovarialkarzinomrezidiv, die auf eine platinhaltige Chemotherapie angesprochen haben, sollte eine Erhaltungstherapie mit Niraparib, Olaparib und Rucaparib angeboten werden. Daten der Zulassungsstudien zu den PARPi sind in Tabelle 1 zusammengefasst.

***Tabelle 1: PARP-Inhibitoren bei Patientinnen mit fortgeschrittenem, mäßig bis undifferenziertem, serösem Ovarialkarzinom nach erneutem Ansprechen auf eine platinhaltige Chemotherapie***

| Studienname / Erstautor / Jahr | Patienten | Kontrolle | Neue Therapie | N[1] | PFÜ[2] (HR[3]) | ÜLZ[4] (HR[3]) |
|---|---|---|---|---|---|---|
| Mirza, 2016 [3], Dossier Nutzenbewertung | gBRCA1/2[5] | Placebo | Niraparib | 203 | 5,5 vs 21,0[6]<br>0,27[7]<br>p < 0,001 | n.e.[8] vs n.e.<br>0,77<br>n.s.[9] |
| | non-gBRCA1/2[5] | Placebo | Niraparib | 350 | 3,9 vs 9,3<br>0,45<br>p < 0,001 | n.e. vs n.e.<br>0,73<br>n.s. |
| Ledermann [4, 5, 6] | Alle | Placebo | Olaparib | 265 | 4,8 vs 8,4<br>0,35<br>p < 0,001 | 27,8 vs 29,8<br>0,73<br>p = 0,021 |
| | mBRCA1/2[5] | Placebo | Olaparib | 136 | 4,3 vs 11,2<br>0,18<br>p < 0,0001 | 30,2 vs 34,9<br>0,62<br>p = 0,021 |
| Coleman [7, 8] | alle | Placebo | Rucaparib | 564 | 5,4 vs 10,8 | n.e vs 29,6 |

**Kontaktdaten**

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) für das Leitlinienprogramm Onkologie (AWMF, Deutsche Krebsgesellschaft, Deutsche Krebshilfe)

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Indikation gemäß Beratungsantrag

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| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | **0,36**<br>**p < 0,0001** | **0,88**<br>**n. s.** |
| | **mBRCA1/2**[5] | **Placebo** | **Rucaparib** | **196** | **5,4 vs 16,6**<br>**0,23**<br>**p < 0,0001** | |
| **Aghajanian, 2012 [9]** | | **Placebo** | **Bevacizumab** | **484** | **8,4 vs 12,4**<br>**0,484**<br>**p < 0,0001** | **56,4 vs 58,2**<br>**0,95**<br>**n. s.** |
| **Coleman, 2017 [10]** | | **-** | **Bevacizumab** | **647** | **10,4 vs 13,8**<br>**0,628**<br>**p < 0,001** | **37,3 vs 42,2**<br>**0,829**<br>**p = 0,056** |

[1] N - Anzahl Patienten; [3] PFÜ - progressionsfreie Überlebenszeit, in Monaten; [3] HR - Hazard Ratio; [4] ÜLZ - Gesamtüberlebenszeit, in Monaten; [5] gBRCA1/2 – BRCA1 und 2 in germline (nicht mutiert), mBRCA1/2 – BRCA1 oder 2 mutiert (Keimbahn oder somatisch), non-gBRCA1/2 – BRCA1 und 2 nicht in germline (mutiert); [6]**Ergebnis für Kontrolle, Ergebnis für Neue Therapie**; [7] **Hazard Ratio in grüner Farbe -** Vorteil für Neue Therapie; [8] n. e. – Median nicht erreicht;[9] n. s. - nicht signifikant;

Wirksamkeit besteht sowohl bei Patientinnen mit BRCA 1/2 Mutationen als auch bei Patientinnen mit Wildtyp (germline).

Die Entscheidung zwischen den Medikamenten sollte nach Erwägung des Nebenwirkungsprofils und der Patientinnenpräferenz erfolgen, da direkt vergleichende Studien zur Wirksamkeit und dem Nebenwirkungsprofil fehlen.

**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der „***Erhaltungstherapie bei erwachsenen Patientinnen mit Rezidiv eines Platin-sensiblen, gering differenzierten serösen Karzinoms der Ovarien, der Tuben oder mit primärer Peritonealkarzinose, die sich nach einer Platin-basierten*

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*Chemotherapie in Remission (komplett oder partiell) befinden*" **die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Von dem og. Vorgehen muss bei Vorliegen von Kontraindikationen oder nicht tolerablen Toxizitäten gegen eine Kombinationschemotherapie, Anti-Angiogenese Antikörper oder PARP Inhibitoren abgewichen werden. Neben dem Alter, Fragilität und Allgemeinzustand wären substanzspezifische zumindest relative Kontraindikationen bei Bevacizumab unter anderem ein nicht kontrollierter Hypertonus, eine frische Embolie oder eine Wundheilungsstörung. Bezüglich der Gabe von Anti-Angiogenese Antikörper oder PARP Inhibitoren müssen diese bei nicht tolerablen Nebenwirkungen ausgesetzt werden.

Andere alternative Erhaltungstherapien existieren zu diesem Zeitpunkt nicht.

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