Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-112 Niraparib

Stand: Juli 2019

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	Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Olaparib (Beschluss vom 6. Dezember 2018) – Erhaltungtherapie - Niraparib (Beschluss vom 7.Juni 2018) – Erhaltungtherapie
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 **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Niraparib L01XX54 Zejula	Zugelassenes Anwendungsgebiet: 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 L01XC07 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. <u>Behandlung des platinsensitiven Rezidivs:</u> 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 L01XA02 Carboplatin Bendalis	Carboplatin ist für die Behandlung folgender Karzinome angezeigt: 1. fortgeschrittenes epitheliales Ovarialkarzinom als: (b) Second-line-Therapie, wenn andere Behandlungen versagt haben
Cisplatin L01XA01 Cisplatin Teva®	Cisplatin Teva® wird angewendet zur Behandlung des: - fortgeschrittenen oder metastasierten Ovarialkarzinoms Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.
Cyclophosphamid L01AA01 Endoxan	Cyclophosphamid ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Fortgeschrittenes Ovarialkarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Doxorubicin L01DB01 Doxorubicinhydrochlorid Bendalis	- fortgeschrittenes Ovarialkarzinom
Doxorubicin *(liposomal)* L01DB01 Caelyx®	Caelyx ist indiziert: - Zur Behandlung von Patientinnen mit fortgeschrittenem Ovarialkarzinom nach Versagen einer platinhaltigen First-Line-Chemotherapie.
Epirubicin L01DB03 Epirubicin onkovis	Epirubicin ist für die Behandlung folgender maligner Erkrankungen in Mono- und Kombinationsschemata angezeigt: - fortgeschrittenes Ovarialkarzinom
Etoposid L01CB01 Vepesid®	VEPESID K ist in Kombination mit anderen zugelassenen Chemotherapeutika angezeigt zur Behandlung des nicht-epithelialen Ovarialkarzinoms bei Erwachsenen.
Gemcitabin L01BCO5 Gemedac®	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.
Olaparib L01XX46 Lynparza®	<u>Ovarialkarzinom</u> Lynparza wird angewendet als Monotherapie für die: - Erhaltungstherapie von erwachsenen Patientinnen mit einem fortgeschrittenen (FIGO-Stadien III und IV) BRCA1/2-mutierten (in der Keimbahn und/oder somatisch), high-grade epithelialen Ovarialkarzinom, Eileiterkarzinom oder primären Peritonealkarzinom, die nach einer abgeschlossenen Platin-basierten Erstlinien-Chemotherapie ein Ansprechen (vollständig oder partiell) haben. - Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines high-grade epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms, die auf eine Platin-basierte Chemotherapie anspreche (vollständig oder partiell).
Melphalan 01AA03 Melphalan-ratiopharm®	Melphalan-ratiopharm® wird in der konventionellen intravenösen Dosierung zur Behandlung des multiplen Myeloms und des Ovarialkarzinoms angewendet. Melphalan-ratiopharm® kann in den oben genannten Anwendungsgebieten allein oder in Kombination mit anderen Zytostatika angewendet werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Niraparib L01XX54 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.
Paclitaxel L01CD01 Paclitaxel-GRY®	Zur Second-line Chemotherapie des Ovarialkarzinoms ist Paclitaxel-GRY bei Patientinnen mit metastasierendem Ovarialkarzinom nach Versagen einer Standardtherapie mit platinhaltigen Arzneimitteln angezeigt.
Paclitaxel L01CD01 Paclitaxel HAEMATO	Ovarialkarzinom: 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. 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 L01XX55 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 L01XX17 HYCAMTIN®	Als Monotherapie ist Topotecan angezeigt zur Behandlung von: - Patientinnen mit metastasierendem Ovarialkarzinom nach Versagen einer Primär oder Folgetherapie.
Trabectedin L01CX01 Yondelis	Yondelis in Kombination mit pegyliertem liposomalem Doxorubicin (PLD) wird angewendet bei Patientinnen zur Behandlung eines platinsensiblen Ovarialkarzinomrezidivs.
Treosulfan L01AB02 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. 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: 2019-B-112 (Niraparib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	The Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard ratio
IQWiG	Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
CI	Confidence interval
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Therapie des vorbehandelten Ovarial-, Eileiter- oder primären Peritonealkarzinoms.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Ovarialkarzinom, Eileiterkarzinom oder Peritonealkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, 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.

Die Recherche ergab 1554 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 23 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **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-

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.

G-BA, 2018 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **Niraparib**

Anwendungsgebiet

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

Niraparib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 11 1. Halbs. SGB V gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der G-BA stuft das Ausmaß des allein aus rechtlicher Sicht nach § 35 a Absatz 1 Satz 11 Halbsatz 1 SGB V zu unterstellenden Zusatznutzens von Niraparib auf Basis der Kriterien in § 5 Absatz 7 der AM-NutzenV unter Berücksichtigung des Schweregrades der Erkrankung und des therapeutischen Ziels bei der Behandlung der Erkrankung derzeit als nicht quantifizierbar ein.

3.2 Cochrane Reviews

Wiggans AJ et al., 2015 [20].

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

Fragestellung

To determine the benefits and risks of PARP inhibitors for the treatment of epithelial ovarian cancer (EOC).

Methodik

Population:

- Women ≥ 18 years old with histologically proven EOC of any stage. We excluded women with other concurrent malignancies

Intervention/Komparator:

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

Endpunkte:

- Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), Quality of life, adverse events

Recherche/Suchzeitraum:

- 1990 to April 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs involving 599 women with EOC (3 studies to Olaparib)
- 1 Study to veliparib

Charakteristika der Population:

- **PARP inhibitor versus conventional chemotherapy (Study: Kaye 2012)**
  - Ninety-seven women with EOC who had relapsed within 12 months of platinum-based chemotherapy (i.e. platinum-resistant and partially platinum-sensitive disease)
  - All included women had BRCA mutations
- **PARP inhibitor versus placebo (as maintenance) (Study: Ledermann 2012)**
  - In women with platinum-sensitive EOC (relapse after six months of previous platinum-based chemotherapy)
  - Participants were required to have received two previous courses of platinum-based chemotherapy, the most recent of which was to have induced an objective response. Arm 1: OLA 400 mg bd maintenance therapy; Arm 2: Placebo tablets bd maintenance therapy. All women within 8 weeks after completion of the last dose of platinum-based chemotherapy.
  - BRCA mutation status was similar in the two groups (around 22%)
- **PARP inhibitor plus conventional chemotherapy versus conventional chemotherapy alone (Studies: Kummar 2015, Oza 2015)**
  - Oza 2015:
    - 41/107 tested (38%) had BRCA mutation
    - Of 162 women randomised, 156 received treatment (platinum based chemo-therapy: 81 olaparib versus 75 placebo) and, of these, 121 began the maintenance/no further therapy phase (66 olaparib versus 55 no maintenance).
    - Oza 2015: Arm A - OLA orally in combination with paclitaxel (P) intravenous (IV) and carboplatin (C); followed by OLA monotherapy maintenance; Arm B - Paclitaxel (P) IV and carboplatin (C) IV; followed by a post-completion phase in which no study treatment was administered.
- Kummar 2015 compared veliparib with cyclophosphamide versus cyclophosphamide alone.
    - The study was closed early due to poor responses observed at interim analysis, when only half the participants had been accrued.

Qualität der Studien:

- We considered studies to be at a low (Ledermann 2012) to moderate (Oza 2015, Kaye 2012) risk of bias (risk mainly due to lack of blinding). We considered one study to be at a high risk of bias as it closed early and remains unpublished (Kummar 2015).

Studienergebnisse:

Overall survival

PARP inhibitor versus placebo (as maintenance) / PARP inhibitor plus conventional chemotherapy versus conventional chemotherapy alone

- 2 studies (426 participants) compared Olaparib versus placebo (Ledermann 2012) or conventional chemotherapy (Oza 2015).
- There was no significant difference in OS when we pooled data from the two studies that included participants with platinum sensitive disease (HR1.05, 95%CI 0.79 to 1.39; I^2 = 0%). We graded this evidence as moderate quality using the GRADE approach.

- The included studies were not powered for OS.

PARP inhibitor versus conventional chemotherapy

- One study (Kaye 2012) compared olaparib to conventional chemotherapy (pegylated liposomal doxorubicin (PLD))
- Ninety-seven women with EOC who had relapsed within 12 months of platinum-based chemotherapy (i.e. platinum-resistant and partially platinum-sensitive disease) were randomised to one of three treatment arms (olaparib200mg, olaparib 400mg, PLD50mg) in a ratio of 1:1:1. HR 0.82 (80%CI 0.52 to 1.31) (in favour of olaparib).

Adverse events/QoL

- Olaparib was associated with more severe adverse events (G3/4) during the maintenance phase compared with controls (risk ratio (RR) 1.74, 95% CI 1.22 to 2.49; 385 participants, two studies; high quality evidence).

Quality of life

- Quality of life was reported as not different between treatment groups in Ledermann 2012 and Kaye 2012 (using FACT-O and TrialOutcome Index) Quality of life data were insufficient for meta-analysis.

Anmerkung/Fazit der Autoren

PARP inhibitors appear to improve PFS in women with recurrent platinum-sensitive disease. Ongoing studies are likely to provide more information about whether the improvement in PFS leads to any change in OS in this subgroup of women with EOC. More research is needed to determine whether PARP inhibitors have any role to play in platinum-resistant disease.

Hinweise

- Veliparib ist in Deutschland nicht zugelassen

3.3 Systematische Reviews

Yi T et al., 2019 [23].

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:

- PARPis 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:

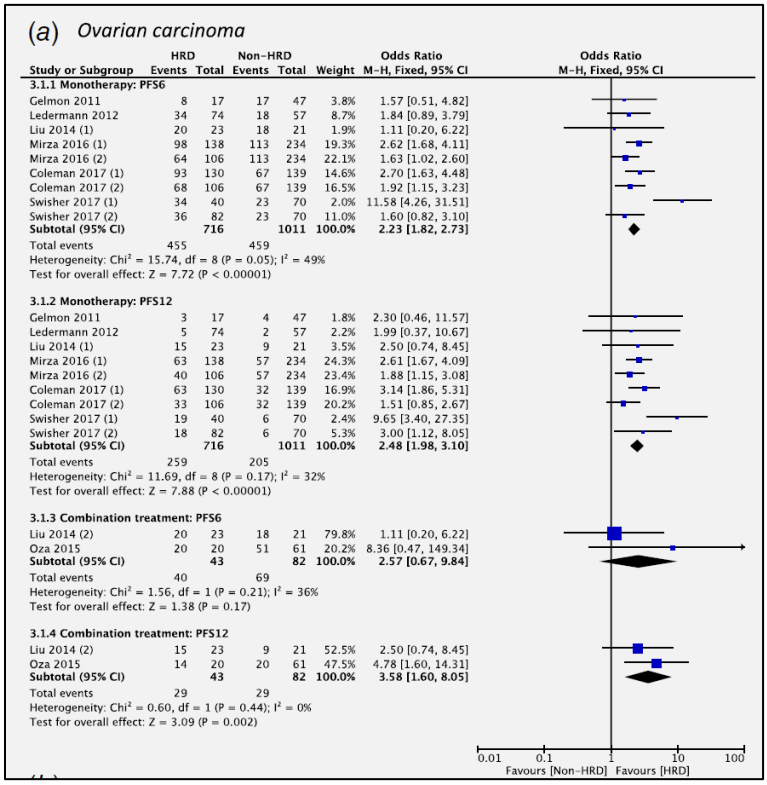
- All clinical trials were international multi-center studies, with intervention group sample sizes ranging from 10 to 431 patients.Qualität der Studien:
- In the interventional arm, PARPis being investigated as monotherapy were: olaparib in 7 studies, rucaparib in 2 studies, and niraparib in 1 study. 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.

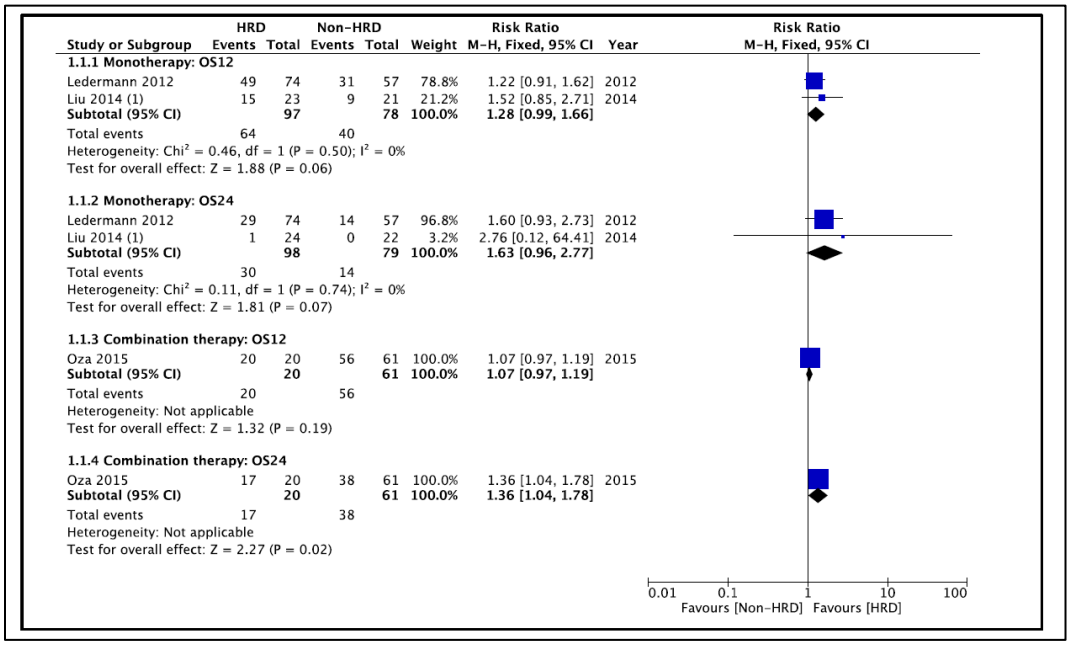
Table 1. Characteristics of included studies for PARP inhibitors

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:

Only subgroup analyses for ovarian carcinoma trials (n = 8) were reported





- As olaparib, rucaparib, and niraparib are approved for use in ovarian cancer as monotherapy, we first focused on this pooled analysis on PARP inhibitors as monotherapy and then applied the same analysis for combination therapies. Six studies (four RCTs and two single-arm trials) contributing nine pairwise subgroups (716 participants in the HRD subgroup and 1,011 participants in the non-HRD subgroup) were incorporated into the meta-analysis for monotherapy. Among them, three trials (Mirza et al.,19 Coleman et al.20 and Swisher et al.11) used two nonoverlapping classification strategies for HRD status in carcinomas based on BRCA mutation or LOH (a feature of HRD). To be consistent, we included these three studies depending on the relevance to our meta-analysis:
  - (1) BRCA mutation vs. BRCA wild-type without HRD;
  - (2) BRCA wild-type with HRD vs. BRCA wild-type without HRD.
- The meta-analysis revealed that the treatment effect of PARPis in PFS6 and PFS12 significantly favored the HRD subgroup with an ORPFS6 of 2.23 (95% CI: 1.82–2.73) and an ORPFS12 of 2.48 (95% CI: 1.98–3.10) in comparison to the non-HRD subgroup. In the subgroup analysis of combination therapy, only two RCTs were eligible with less statistical power to address this question. We observed no significant differences on PFS6 for HRD vs. non-HRD but a significant improvement in PFS12 favoring the HRD subgroup with an ORPFS12 of 3.58 and a wide 95% CI (1.60–8.05). Importantly, there was no considerable heterogeneity across studies. One-way sensitivity analysis indicated that removing studies one by one from the analysis did not modify the pooled effect estimates. Therefore, in the context of evaluating PARPis as monotherapy, we observed significant association between HRD and improvements in PFS6 and PFS12.

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.

HRD as a predictive biomarker will be a powerful tool for guiding decision-making based on patients' genetic status.

Wang H et al., 2018 [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)

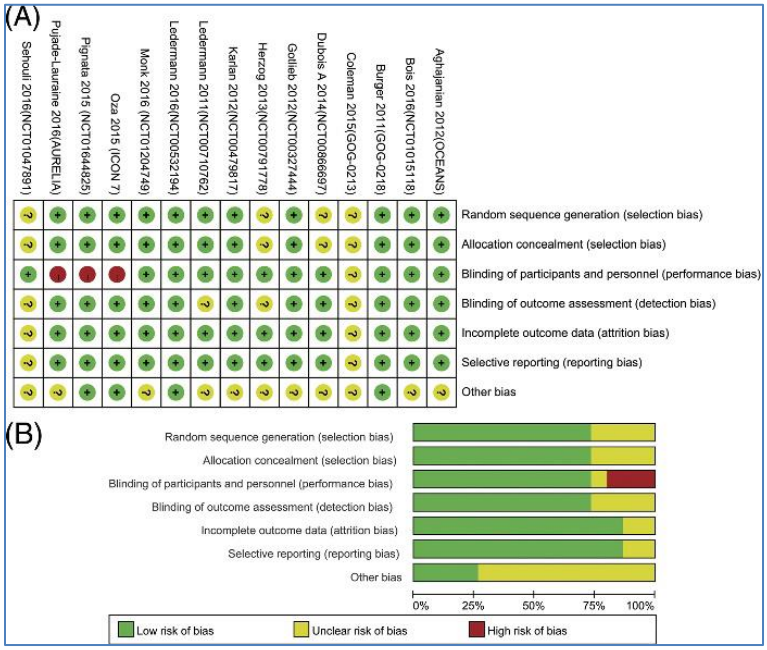
Charakteristika der Population:

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		
Bois et al, 2016 (AGO-OVAR 12)[24]	TC + nintedanib + nintedanib(m)	911	Newly diagnosed,	PFS	17.2	0.84	0.72–0.98	34	0.99	0.77–1.27
	TC + PL + PL(m)	455			16.6			32.8		
Ledermann et al, 2011[25]	BIBF1120	43	Pure maintenance	PFS rate at 36 wks	NA	0.65	0.41–1.02	NA	0.84	0.51–1.39
	PL	40			NA			NA		
Monk et al, 2016 (TRINOVA-1)[26]	PAC + trebananib	461	Recurrent disease	PFS	7.2	0.66	0.57–0.77	19.3	0.95	0.81–1.11
	PAC + PL	458			5.4			18.3		
Karlan et al, 2012[18]	PAC + AMG386 (10 mg/kg)	53	Recurrent	PFS	7.2	0.76	0.49–1.18	22.5	0.60	0.34–1.06
	PAC + PL	55			4.6			20.9		
Karlan et al, 2012[18]	PAC + AMG 386 (3 mg/kg)	53	Recurrent	PFS	5.7	0.75	0.48–1.17	20.4	0.77	0.45–1.31
	PAC + PL	55			4.6			20.9		
Pignata et al, 2015 (MTO-11)[27]	PAC + pazopanib	37	Platinum-resistant recurrent	PFS	6.35	0.42	0.25–0.69	19.1	0.6	0.32–1.13
	PAC	36			3.49			13.7		
du Bois et al, 2014[28]	Pazopanib	472	Pure maintenance	PFS	17.9	0.77	0.64–0.91	NA	1.08	0.87–1.33
	PL	468			12.3			NA		
Sehouli et al, 2016[17]	TOP + sorafenib	86	Platinum-resistant or refractory recurrent	PFS	6.7	0.6	0.43–0.83	17.1	0.65	0.45–0.93
	TOP + PL	86			4.4			10.1		
Herzog et al, 2013[29]	Sorafenib	123	Pure maintenance	PFS	12.7	1.09	0.72–1.63	NA	1.49	0.69–3.23
	PL	123			15.7			NA		

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

- Nine studies (n = 3310 participants) assessed the risk of death in the recurrent setting, pooling the data of these studies also found statistically significant lower risk of death in women who received antiangiogenics-containing combination therapies compared with thosewho received chemotherapy alone (HR, 086; 95% CI, 0.79-0.94; I2 = 0%).
- In addition, further subgroup analysis showed 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, 0.76Y0.98; I2 = 0%) and platinum-resistant recurrent ovarian cancer from 4 trials with a total of 661 participants (HR, 0.78; 95% CI, 0.65-0.94; I2 = 0%).
- Conversely, no significant difference in the risk of death was observed in the pure maintenance antiangiogenics therapy who achieved a good response to before chemotherapy (HR, 1.06; 95% CI, 0.88-1.28; I2 = 0%) based on the results of 3 studies with a total of 1269 patients (Fig. 3a).

Progression-Free Survival

- Angiogenesis inhibitors and chemotherapy combination treatment had significantly lower risks of disease progression compared with women with chemotherapy alone in the recurrent setting (HR, 0.58; 95% CI, 0.52-0.65; I2 = 39%).
- 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%) and platinum-resistant recurrent ovarian cancer (HR, 0.50; 95% CI, 0.42-0.60; I2 = 0%) both suggested significantly lower risks of disease progression. We detected no significant heterogeneity in both subgroups.
- However, although pazopanib showed a significantly improved PFS (HR, 0.76; 95% CI, 0.64-0.91) from 1 trial,28 we found no significant improvement for PFS in the pure maintenance angiogenesis inhibitors therapy (HR, 0.80; 95% CI, 0.63-1.01; I2 = 37%), with no significant between-study heterogeneity

Anmerkung/Fazit der Autoren

Although women with advanced epithelial ovarian cancer responded to many available therapeutic agents, almost all die from recurrence, which makes the treatment of recurrent ovarian cancer important. In the present study, antiangiogenics-containing therapies significantly reduced theHRof progression by 42% and risk of death by 14%, comparedwith chemotherapy alone with no significant between-study heterogeneity. Further analysis of 2 subgroups (ie, platinum-sensitive recurrent ovarian cancer and platinum-resistant recurrent ovarian cancer) both showed improvement on PFS and OS, with no significant between-study heterogeneity. The results were encouraging among women with recurrent ovarian cancer

nomatterwhether responded to previous platinum-containing chemotherapy or not, demonstrating that angiogenesis inhibitors combined with chemotherapy is a great treatment option for recurrent ovarian cancer. Among them, bevacizumab, a kind of antiangiogenics by binding VEGF, has demonstrated a significant clinical benefit from several trials, and on the basis of these trials, bevacizumab was approved for first-line and second-line treatment of patients with both platinum-sensitive and platinum-resistant ovarian cancer.26 However, its activity in patients whose disease relapses after first-line bevacizumabcontaining therapy is still unknown. Hence, further studies addressing this issue need to be performed.

Maintenance therapy has been one proposed strategy to improve outcomes, and incorporation of angiogenesis inhibitors had also been of interest. Recently, a number of clinical trials took combined strategies, using angiogenesis inhibitors in the maintenance setting. In the present study, we mainly analysed the maintenance antiangiogenics monotherapy in the trials, which recruited patients who responded to previous chemotherapy (ie, a Partial Response or Complete Response according to the RECIST criteria in patients with measurable disease). In the trial,25 BIBF 1120 was not given to treat recurrent disease but to prolong the progression-free interval. It was evaluated after the completion of chemotherapy for relapsed ovarian cancer. The other 2 trials28,29 were designed to compare pazopanib or sorafenib to placebo as maintenance treatment after first-line therapy with systemic chemotherapy, and pazopanib showed a significant better PFS in the maintenance setting. However, pooled analysis of the 3 studies suggested no significant improvement in either PFS or OS.

The lack of statistical significance may be because of lack of statistical power. In addition, more patients in the experience arm required dose modifications and discontinued treatment because of severe AEs, such as severe liver-related toxicity, severe gastrointestinal events, resulting in reduced dose of the planned dose. As a group, both short-term and longer-term adverse effects, the negative impact on quality of life associated with frequent visits to a physician or clinic and the cost may resulting in no significantly clinical benefit. Hence, further study should be performed to select patients who can really benefit from longterm maintenance treatment, particularly those who are at high risk of progression.

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 combinationwith chemotherapy in the clinicalmanagement 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.

Hinweise:

Results for newly diagnosed ovarian cancer are not reported.

Ruan G et al., 2018 [14].

The role of bevacizumab in targeted vascular endothelial growth factor therapy for epithelial ovarian cancer: an updated systematic review and meta-analysis

Fragestellung

We systematically review published data and comprehensively analyze and integrate all published Phase III RCTs to evaluate the efficacy of bevacizumab combinations with different regimens, regardless of first-line treatment or recurrent disease, in patients with EOC.

Methodik

Population:

- Patients with epithelial ovarian cancer (EOC)

Intervention/ Komparator:

- bevacizumab added as maintenance therapy after chemotherapy, or concurrently with chemotherapy followed by a maintenance period

Endpunkte:

- PFS and OS, toxicity or adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, Chinese Knowledge Infrastructure (CNKI), and the Cochrane Central Register of Controlled Trials (CENTRAL) on or before June 26, 2017 in English or Chinese

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 studies (n=4994)

Charakteristika der Population:

Table 1 Characteristics of included studies

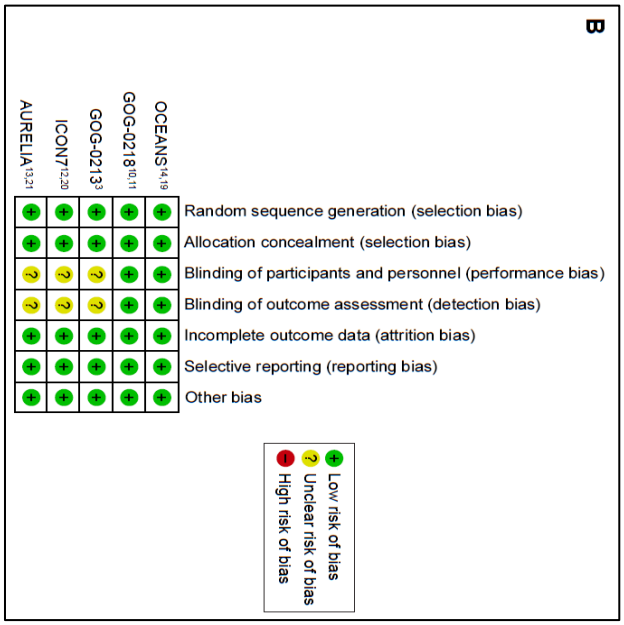
Study	Diagnostic criteria	GOG/ECOG PS	Setting	n	Treating arm	Median age (range)
GOG-0218[10,11]	GOG	GOG PS 0–2	First-line and maintenance	625	P + C + PL; PL maintenance	60 (25–86)
				625	P + C + Bev; PL maintenance	60 (24–88)
				623	P + C + Bev; Bev maintenance	60 (22–89)
ICON7[12,20]	Local histopathological findings	ECOG PS 0–2	First-line and maintenance	764	P + C	57 (18–81)
				764	P + C + Bev; Bev maintenance	57 (24–82)
OCEANS[14,19]	NR	ECOG PS 0–1	Recurrent, platinum-sensitive	242	G + C + P (combination and maintenance)	61 (28–86)
				242	G + C + Bev (combination and maintenance)	60 (38–87)
AURELIA[13,21]	NR	ECOG PS 0–2	Recurrent, platinum-resistant	182	PAC or T or PLD	61 (25–84)
				179	PAC or T or PLD + Bev	61 (25–80)
GOG-0213[3]	NR	GOG PS 0–2	Recurrent, platinum-sensitive	374	P + C	60
				374	P + C + Bev; Bev maintenance	

Abbreviations: P, paclitaxel; C, carboplatin; Bev, bevacizumab; G, gemcitabine; T, topotecan; PLD, pegylated liposomal doxorubicin; PAC, weekly paclitaxel; PL, placebo; GOG, Gynaecologic Oncology Group; ECOG, Eastern Cooperative Oncology Group; AUC, area under curve; PS, performance status; NR, not reported.

Qualität der Studien:

Five published studies[3,11–14] showed a low risk of bias in randomized sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases;

meanwhile, blinding exhibited a low risk of bias in two published studies[11,14] and was unclear in three open-label published studies.[3,12,13]



Studienergebnisse:

Bevacizumab plus chemotherapy improved progression-free survival (hazard ratio [HR] =0.63; 95% confidence interval [CI], 0.51–0.77; P=0.01) and overall survival (HR =0.91; 95% CI, 0.84–0.99; P=0.05). Interestingly, in patients with a high risk of progression, the subgroups that received bevacizumab combined with different regimens of chemotherapy showed a significant improvement with paclitaxel plus carboplatin-based chemotherapy (HR =0.86; 95% CI, 0.77–0.95; P=0.01), but not with non-paclitaxel plus carboplatin-based chemotherapy (HR =0.91; 95% CI, 0.77–1.07; P.0.05) in overall survival.

Anmerkung/Fazit der Autoren

The combination of bevacizumab with a PC-based regimen offers a new treatment option for patients with EOC, especially in those with a high risk of progression.

Li X et al., 2016 [11].

Angiogenesis inhibitors for patients with ovarian cancer: a meta-analysis of 12 randomized controlled trials

Siehe auch:

Ding SS et al., 2014 [1]. Systematic evaluation of bevacizumab in recurrent ovarian cancer treatment

Li J et al., 2015 [10]. Addition of bevacizumab to chemotherapy in patients with ovarian cancer: a systematic review and meta-analysis of randomized trials

Miao H et al., 2017 [12]. Does the age affect the efficacy of angiogenesis inhibitors in ovarian cancer? A meta-analysis of randomized controlled trials

Fragestellung

This meta-analysis aimed to evaluate the efficacy of angiogenesis inhibitors, concurrent with chemotherapy and continued for a maintenance period (the throughout strategy) or maintenance after chemotherapy (the maintenance strategy), in patients with advanced or recurrent epithelial ovarian cancer.

Methodik

Population:

- Advanced ovarian cancer

Intervention/Komparator:

- anti-angiogenic targeted agents were used as maintenance therapy after chemotherapy, or concurrently with chemotherapy followed by a maintenance period

Endpunkte:

- PFS,OS

Recherche/Suchzeitraum:

- PubMed and Embase databases and the Cochrane library published between January 2000 and June 2015

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 trials comprising four phase II trials[13–16] and eight phase III trials[4–7,11,12,17,18] met the inclusion criteria of this meta-analysis, and 7775 patients were included in the assessment of OS, PFS, and toxicity

Charakteristika der Population:

Twelve trials included six inhibitors were divided into three types according to different targets of activity: four trials with a VEGF inhibitor (the bevacizumab group)[4–7], six trials with VEGFR inhibitors (the VEGFRIs group)[11–13,15,16,18,] and two trials with an angiopoietin inhibitor (the trebananib group)[14,17]

First Author Year/Phase	Patient Stage	Intervention Group	Control Group	HR (95% CI)	
				PFS	OS
Burger RA[4] 2011/III	III or IV	Carboplatin + paclitaxel + bevacizumab, every 3 weeks for 6 cycles Followed by bevacizumab for 16 cycles	Carboplatin + paclitaxel, every 3 weeks for 6 cycles	0.72 (0.63–0.82)	0.92 (0.73–1.15)
Perren TJ[5] 2011/III	I–II (9%) III–IV (91%)	Carboplatin + paclitaxel + bevacizumab, every 3 weeks for 5 or 6 cycles Followed by bevacizumab for 12 cycles	Carboplatin + paclitaxel, every 3 weeks for 6 cycles	0.81 (0.70–0.94)	0.85 (0.69–1.04)
Aghajanian C[6] 2012/III	Recurrent	Carboplatin + gemcitabine + bevacizumab, every 3 weeks for 6 to 10 cycles Followed by bevacizumab until disease progressed	Carboplatin + gemcitabine, every 3 weeks for 6 to 10 cycles	0.48 (0.39–0.61)	1.03 (0.79–1.33)
Pujade-Lauraine E[7] 2014/III	Recurrent	Single-agent chemotherapy + bevacizumab until disease progressed	Single-agent chemotherapy until disease progressed	0.48 (0.38–0.60)	0.85 (0.66–1.08)
du Bois A[18] 2014/III	II (7%) III–IV (93%)	Platinum–taxane-based chemotherapy, at least 5 cycles Followed by pazopanib until disease progressed	Platinum–taxane-based chemotherapy, at least 5 cycles	0.77 (0.64–0.91)	1.08 (0.87–1.33)
Monk BJ[17] 2014/III	Recurrent	Paclitaxel + trebananib until disease progressed	Paclitaxel until disease progressed	0.66 (0.57–0.77)	0.86 (0.69–1.08)
Karlan BY[14] 2012/II	Recurrent	Paclitaxel + trebananib until disease progressed	Paclitaxel until disease progressed	0.76 (0.52–1.12)	0.60 (0.34–1.06)
du Bois A[12] 2013/III	III or IV	Carboplatin + paclitaxel + nintedanib for 6 cycles Followed by nintedanib until disease progressed	Carboplatin + paclitaxel + nintedanib for 6 cycles	0.84 (0.72–0.98)	0.99 (0.77–1.27)
Ledermann JA[15] 2011/II	Recurrent	Second line chemotherapy Followed by nintedanib until disease progressed	Second line chemotherapy	0.65 (0.41–1.02)	0.84 (0.51–1.39)
Ledermann JA[11] 2013/III	Recurrent	Platinum-based chemotherapy and cediranib for six cycles Followed by cediranib until disease progressed	Platinum-based chemotherapy	0.57 (0.45–0.74)	0.70 (0.51–0.99)
Herzog TJ[13] 2013/II	III or IV	Platinum + taxane for first line chemotherapy Followed by sorafenib until disease progressed	Platinum + taxane for first line chemotherapy	1.09 (0.72–1.63)	1.49 (0.69–3.23)
Pignata S[16] 2015/II	Recurrent	Paclitaxel + pazopanib until disease progressed	Paclitaxel until disease progressed	0.42 (0.25–0.69)	0.60 (0.32–1.13)

Table 2. Anti-angiogenic agents in randomized clinical trials.

Drug	Targets	Study	No.	Intervention
Bevacizumab	VEGF	GOG-218	1873	Frontline followed by a maintenance period
		ICON-7	1528	Frontline followed by a maintenance period
		OCEANS	484	Second line followed by a maintenance period
		AURELIA	361	Second line followed by a maintenance period
Pazopanib	VEGFR-1, -2, and -3 PDGFR-α and -β c-Kit	AGO-OVAR 16	940	Maintenance after frontline
		MITO 11	74	Second line followed by a maintenance period
Trebananib	Ang-1 and -2	TRINOVA-1	919	Frontline followed by a maintenance period
		NCT00479817	160	Second line followed by a maintenance period
Nintedanib	VEGFR-1, -2 and -3 PDGFR-α and -β FGFR-1, -2 and -3 Src and FLT-3	AGO-OVAR 12	1352	Frontline followed by a maintenance period
		NCT00710762	83	Maintenance after second line
Cediranib	VEGFR-1, -2 and -3	ICON6	456	Second line followed by a maintenance period
Sorafenib	VEGFR-2 and -3 PDGFR-β	NCT00791778	246	Maintenance after frontline

Qualität der Studien:

The quality was high in all the studies (Jadad score ≥3).

Studienergebnisse:

Progression-free survival and overall survival

- Compared with chemotherapy alone, improvement of PFS was seen in all three groups (HR=0.61, 95% CI 0.48 to 0.79, P50.001 for bevacizumab; HR=0.71, 95% CI 0.59 to 0.87, P=0.001 for VEGFRIs; and HR=0.67, 95% CI 0.62 to 0.72, P50.001 for trebananib)
- Regarding OS, bevacizumab showed a trend of improvement although without significance (HR=0.90, 95% CI 0.80 to 1.01, P=0.079), VEGFRIs showed no improvement (HR=0.92. 95% CI 0.75 to 1.11, P=0.368), and trebananib demonstrated a significant prolongation (HR=0.81, 95% CI 0.67 to 0.99, P=0.036)

- Combining all three groups together, a significant reduction (10%) in the hazard of death (HR=0.90, 95% CI 0.83 to 98, P=0.014) was found.
- when compared with chemotherapy alone, anti-angiogenic therapy showed improvement in three sub-groups, namely phase III trials (HR=0.91, 95% CI 0.84 to 0.99, P=0.036), the throughout strategy (HR=0.87, 95% CI 0.79 to 0.95, P=0.002), and second line treatment (HR=0.85, 95% CI 0.75 to 0.95, P<0.001). For PFS, the survival benefit was consistently seen across all defined subgroups.

Table 3. Sub-group analysis for PFS and OS.

Sub-group	No. of trials	PFS HR (95% CI)	OS HR (95% CI)
Phase			
II	4	0.72 (0.59–0.89)	0.77 (0.60–1.00)
III	8	0.68 (0.65–0.72)	0.91 (0.84–0.99)
Strategy			
Throughout	9	0.68 (0.64–0.71)	0.87 (0.79–0.95)
Maintenance	3	0.81 (0.69–0.95)	1.06 (0.88–1.28)
Timing			
First line	4	0.78 (0.72–0.84)	0.95 (0.85–1.06)
Second line	8	0.63 (0.59–0.67)	0.85 (0.75–0.95)

Toxicity

- Overall, treatment including angiogenesis inhibitors was associated with a greater incidence of drug-related grade 3 or higher toxic effects. In group 1, class-specific adverse events (AEs) caused by bevacizumab were hypertension, proteinuria, wound-healing complications, thrombotic events, and gastrointestinal perforations.
- The relative risk (RR) for the class-specific adverse events was 4.05 (95% CI 1.99 to 8.27, P<0.001; I2=88.1%, P<0.001). The most common bevacizumab related grade 3 or higher toxicities were hypertension (RR=58.52, 95% CI 23.84 to 143.65, P<0.001; I2=0%, P=0.525) and proteinuria (RR=4.50, 95% CI 2.00 to 10.12, P<0.001; I2=37.5%, P=0.202).
- The four VEGFR inhibitors were all associated with AEs of grade 3 or greater such as hypertension (RR=7.75, 95% CI 5.15 to 11.66, P<0.001; I2=0%, P=0.932), diarrhea (RR=8.80, 95% CI 5.35 to 14.48, P<0.001; I2=44.8%, P=0.143), and fatigue (RR=2.78, 95% CI 1.50 to 5.17, P=0.001; I2=6.9%, P=0.359).
- However, toxicity profile differed among the four inhibitors. Hematologic and hepatic toxicity were main the AEs for pazopanib and nintedanib. Hand–foot syndrome and rash were more common for sorafenib as previously reported. And cediranib was associated with higher incidences of hypothyroidism (12%) and hoarseness (10%). In group 3, edema was reported as the most significant trebananib related toxicity. In the phase II and phase III trials, the incidences of any grade edema were 60% and 64%, compared to 22% and 28% in the placebo arm, respectively. The RR for edema of grade 3 or higher was 2.60 (95% CI 0.84 to 8.00, P=0.097; I2=38.5%, P=0.197).

Anmerkung/Fazit der Autoren

In conclusion, angiogenesis inhibitors showed PFS benefit in patients with advanced ovarian cancer. It is important to identify predictive factors to optimize patient selection to obtain OS improvement

Hinweise:

- Trebananib is not approved in Germany.

Wu Y et al., 2017 [21].

Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials

Fragestellung

In this present study, the final data and a new RCT (GOG-213) were included to reassess the efficacy and safety of bevacizumab combined with chemotherapy in ovarian cancer.

Methodik

Population:

- Patients with ovarian cancer

Intervention:

- bevacizumab plus chemotherapy

Komparator:

- chemotherapy

Endpunkte:

- OS, PFS, adverse events

Recherche/Suchzeitraum:

- May 2016 (Pubmed, EMBASE, Web of Science and Central)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien::

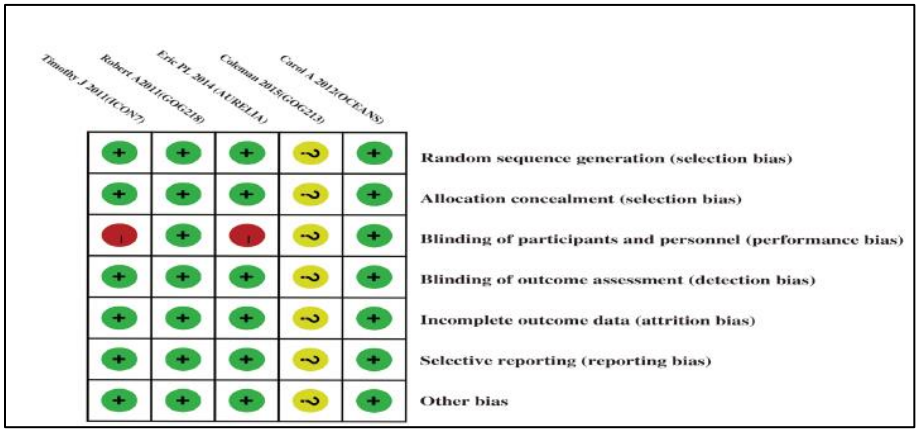
- 5 RCTs (n=4994)

Charakteristika der Population:

Table 1: Characteristics of 5 RCTs

	GOG218	ICON7	OCEANS	AURELIA	GOG213
Primary endpoint	PFS	PFS	PFS	PFS	OS
Patients enrolled	Stage III (incompletely resectable) or stage IV	Stage I-III or StageIV or Inoperable Stage III	Platinum-sensitive recurrent ovarian cancer (recurrence ≥6 months after completing platinum-based therapy)	Platinum-resistant recurrent ovarian cancer that had progressed ≤6 month after completing platinum-based therapy	Platinum-sensitive recurrent ovarian cancer
GOC/ECOG PS	GOG PS 0-2	ECOG PS 0-2	ECOG PS 0-1	ECOG PS 0-2	GOG PS 0-2
Sample size	1248	1528	484	361	748
Average age (year)	60	57	61	61	60
Histology	Epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer	Epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer	Epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer	Epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer	Epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer
Control arm	Cycles 1–6: C (AUC 6) + P (175 mg/m²)+ PL, q3w Cycles 7–22: PL, q3w	Cycles 1–6: C (AUC 5 or 6)+ P (175 mg/m²), q3w	Cycles 1–10: G (1,000 mg/m² on days 1 and 8) + C (AUC 4 on day 1) + PL (15 mg/kg on day 1), q3w	Cycles 1-PD: PAC (80 mg/m² days 1, 8, 15, and 22 q4w); or TOP (4 mg/m², days 1, 8, 15 q4w or 1.25 mg/m², days 1–5 q3w); or PLD (40 mg/m2 day 1 q4w)	Paclitaxel (175 mg/m²) + Carboplatin (AUC5)
Experimental arm	Cycles 1–6: C (AUC 6) + P (175 mg/m²) + Bev (15 mg/kg), q3w Cycles 7–22: Bev (15 mg/kg), q3w	Cycles 1–6: C (AUC 5 or 6)+ P (175 mg/m²)+ Bev (15 mg/kg), q3w Cycles 7–18: Bev (15 mg/kg), q3w	Cycles 1–10: G (1,000 mg/m² on days 1 and 8) + C (AUC 4 on day 1) + Bev (15 mg/kg on day 1), q3w	Cycles 1-PD: Chemotherapy + Bev (15 mg/kg q3w or 10 mg/kg), q2w	Bev (15 mg/kg) + P (175 mg/m²) + C (AUC5), followed by Bev maintenance

Qualität der Studien:



Studienergebnisse:

OS

- 3 RCTs; Bevacizumab had a significantly better OS in the recurrent setting (HR 0.87, 95% CI 0.77-0.99, I2 = 0%)

PFS

3 RCTs, contrast, PFS was significantly improved in the recurrent setting (HR 0.53, 95% CI 0.45-0.63, p = 0.12, I2 = 54%).

Adverse events

Among this updated analysis, the risks of hypertension, proteinuria, bleeding, wound healing disruption, GI perforations, arterial thrombosis events and venous thrombosis events were significantly increased as follows:

- hypertension (risk ratio (RR) 21.27, 95% CI 9.42-48.02, I2 = 0%),
- proteinuria (RR 4.77, 95% CI 2.15-10.61, I2 = 0%),
- wound healing disruption (RR 3.55, 95% CI 1.09-11.59, I2 = 0%),
- bleeding (RR 3.16, 95% CI 1.59-6.30, I2 = 0%),
- GI perforations (RR 2.76, 95% CI 1.51-5.03, I2 = 0%),
- arterial thrombosis events (RR 2.39, 95% CI 1.39-4.10, I2= 14%),
- venous thrombosis events (RR 1.43, 95% CI 1.04-1.96, I2 = 39%)

Anmerkung/Fazit der Autoren

This updated meta-analysis indicates that bevacizumab combined with chemotherapy significantly improved PFS and OS in both patients with high-risk of progression and patients with recurrent OC, with an increased incidence of common adverse events.

Yi Y et al., 2017 [22].

Antiangiogenic drugs used with chemotherapy for patients with recurrent ovarian cancer: a meta-analysis

Fragestellung

This meta-analysis aimed to estimate the efficacy and toxicity of various antiangiogenic drugs for the treatment of patients with recurrent ovarian cancer.

Methodik

Population:

- patients with recurrent ovarian cancer, including platinum-sensitive and platinum-resistant patients

Intervention/ Komparator:

- chemotherapy interventions with or without antiangiogenic drugs

Endpunkte:

- PFS, OS, AE

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were comprehensively searched from January 2000 to May 2016

Qualitätsbewertung der Studien:

- Cochrane irsk of bias tool

Studienergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs (N=3211) with recurrent ovarian cancer
- 3 groups according to the different active targets of the antiangiogenic drugs: 3 RCTs with VEGFRIs,[4–6] 3 RCTs with VEGF inhibitors,[7–9] and 2 RCTs with angiopoietin inhibitors.[10,11]
- One RCT applied antiangiogenic drugs during the maintenance phase,4 but the other drugs were fully employed from the beginning of therapy to disease progression in the other 7 RCTs.

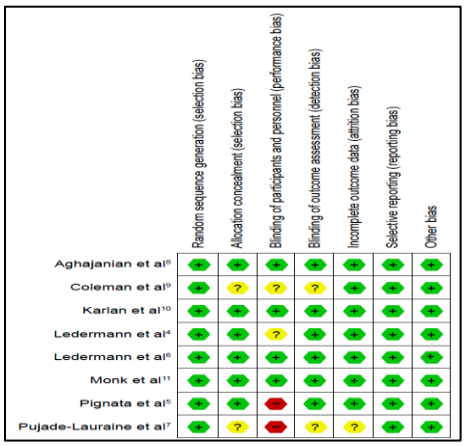
Charakteristika der Population:

Table 1 The basic characteristics of the included randomized controlled trials

Reference	Agent type	Median age (years)	Sample size (n)	Platinum (sensitive/resistant) (n)		Histologic type (n)	Intervention group	Control group
		Exp/Con	Exp/Con	Exp	Con	Exp/Con		
Ledermann et al[4]	VEGFRIs	60/63	43/40	26/17	23/17	Serous (34/35) Mucinous (1/0) Endometrioid (0/1) Clear cell (0/2) Others (8/1) Missing (0/1)	Chemotherapy followed by nintedanib maintenance	Chemotherapy followed by placebo
Pignata et al[5]	VEGFRIs	56/58	37/36	0/37	1/35	Serous (26/24) Mucinous (1/0) Endometrioid (4/2) Undifferentiated (3/1) Clear cell (1/3) Mixed (0/3) Transitional (1/2) Mixed Mullerian (1/1)	Paclitaxel + pazopanib until disease progressed	Paclitaxel until disease progressed
Ledermann et al[6]	VEGFRIs	62/62	338/118	338/0	118/0	Serous (245/87) Mucinous (4/0) Endometrioid (16/3) Undifferentiated (2/3) Clear cell (13/3) Others (56/21) Not available (2/1)	Platinum-based chemotherapy + cediranib for 6 cycles followed by cediranib or placebo maintenance	Platinum-based chemotherapy + placebo for 6 cycles followed by placebo maintenance
Pujade-Lauraine et al[7]	VEGF inhibitor	62/61	179/182	0/179	0/182	Serous (156/152) Endometrioid (8/9) Clear cell (4/12)	Single-agent chemotherapy + bevacizumab until disease progressed	Single-agent chemotherapy until disease progressed
Aghajanian et al[8]	VEGF inhibitor	60.5/61.5	242/242	242/0	242/0	Serous (189/202) Mucinous (3/1) Endometrioid (13/16) Transitional cell (2/2) Clear cell (9/6) Mixed (6/5) Others (20/10)	Carboplatin + gemcitabine + bevacizumab for 6–10 cycles followed by bevacizumab maintenance	Carboplatin + gemcitabine for 6–10 cycles
Coleman et al[9]	VEGF inhibitor	60/60	335/339	335/0	339/0	Unclear	Carboplatin + paclitaxel + bevacizumab followed by bevacizumab maintenance	Paclitaxel + carboplatin
Karlan et al[10]	Angiopoietin inhibitor	60/62	106/55	54/51	30/24	Serous (53/34) Endometrioid (13/3) Clear cell (1/2) Mucinous (1/1) Unclassified (33/13) Unavailable (5/2)	Paclitaxel + trebananib until disease progressed	Paclitaxel until disease progressed
Monk et al[11]	Angiopoietin inhibitor	60/59	461/458	223/238	212/246	Serous (385/388) Endometrioid (29/26) Undifferentiated (15/10) Transitional (4/2) Others (28/32)	Paclitaxel + trebananib until disease progressed	Paclitaxel until disease progressed

Abbreviations: Exp, experiment group; Con, control group; VEGFRIs, vascular endothelial growth factor receptor inhibitors; VEGF, vascular endothelial growth factor.

Qualität der Studien:



Studienergebnisse:

PFS

- PFS improved significantly in all the groups, as follows: HR: 0.55, 95% CI: 0.45–0.67, I2=0%, P<0.00001 for the VEGFRI group; HR: 0.53, 95% CI: 0.45–0.63, I2=51%, P<0.00001 for the VEGF inhibitor group; and HR: 0.67, 95% CI: 0.58–0.77, I2=0%, P<0.00001 for the trebananib group.
- PFS improved significantly both the platinum-resistant and the platinum-sensitive recurrent ovarian cancer (HR: 0.47, 95% CI: 0.38–0.58, I2=0%, P<0.00001 for the platinum-resistant group; HR: 0.56, 95% CI: 0.50–0.63, I2=26%, P,0.00001 for the platinum-sensitive group).

OS

- OS was obviously prolonged in the VEGFRI (HR: 0.76, 95% CI: 0.59–0.97, I_2=0%, P=0.03), the VEGF inhibitor group (HR: 0.87, 95% CI: 0.77–0.99, I_2=0%, P=0.03), and the trebananib group (HR: 0.81, 95% CI: 0.67–0.99, I2=0%, P=0.04).
- OS was clearly better in the platinum-sensitive group (HR: 0.86, 95% CI: 0.76–0.99, P=0.03), with no obvious statistical significance for OS in the platinum-resistant group (HR: 0.81, 95% CI: 0.65–1.02, I2=2%, P=0.07).

Adverse Events

- Toxicity (adverse effect grade ≥3, except gastrointestinal perforation [GI P] grade ≥1)
- The incidences of grade 3/4 toxicity were higher when compared with chemotherapy alone but were manageable.
- The proteinuria (RR: 15.64, 95% CI: 4.87–50.23, I2=0%, P,0.00001), hypertension (RR: 12.44, 95% CI: 3.62–42.79, I2=32%, P,0.0001), arterial thromboemboli (RR: 4.84, 95% CI: 1.24–18.91, I2=0%, P=0.02), and GIP (RR: 3.62, 95% CI: 2.09–6.26, I2=0%, P<0.00001) were significantly different.
- rates of hypertension (RR: 3.68, 95% CI: 1.49–9.07, *I*2=0%, *P*=0.005), fatigue (RR: 2.08, 95% CI: 1.11–3.87, *I*2=0%, *P*=0.02), and diarrhea (RR: 5.31, 95% CI: 1.75–16.16, *I*2=0%, *P*=0.003) were numerically higher in the VEGFRI treatment group. In addition, the nintedanib as a VEGFRI was associated with higher incidences of hepatotoxicity (RR: 20.47, 95% CI: 2.89–144.88, *P*=0.003).

- With regard to the VEGF inhibitor group, the proteinuria (RR: 15.64, 95% CI: 4.87–50.23, *I*2=0%, *P*,0.00001), hypertension (RR: 12.44, 95% CI: 3.62–42.79, *I*2=32%, *P*<0.0001), arterial thromboemboli (RR: 4.84, 95% CI: 1.24–18.91, *I*2=0%, *P*=0.02), and GIP (RR: 3.62, 95% CI: 2.09–6.26, *I*2=0%, *P*,0.00001) were significantly different
- trebananib treatment may cause a higher risk of hypokalemia (RR: 2.25, 95% CI: 1.16–4.35, *I*2=0%, *P*=0.02).

Anmerkung/Fazit der Autoren

The antiangiogenic therapy showed a clear improvement in the PFS in the treatment of relapsed ovarian cancer patients. In addition, the bevacizumab and trebananib groups showed prolonged OS. Antiangiogenesis as a targeted therapy seems to be promising, despite the many uncertainties put forth in our study.

Staropoli N et al., 2016 [16].

Is ovarian cancer a targetable disease? A systematic review and meta-analysis and genomic data investigation

Fragestellung

The aim of this work is to provide answer to the basic question if available literature actually supports the concept that molecular targeted agents indeed represent valuable tools for the treatment of EOC. In this light, we attempted to identify the relevance of single targeted pathway in molecularly unselected EOC patients and in several subgroups recognized by clinical criteria.

Methodik

Population:

- Patients with diagnosis of EOC

Intervention:

- targeted therapy-based schedule

Komparator:

- conventional schedule for disease stage

Endpunkte:

- OS, PFS, RR

Recherche/Suchzeitraum:

- PubMed, Embase, and the Central Registry of Controlled Trials of the Cochrane Library, major meeting proceeding databases. January 2004 and June 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 30 studies (n=10530 patients)

Charakteristika der Population:

- 19 were eligible for OS analysis (among them, we underlined, that: 10 were included in anti-angiogenetic analysis; 3 studies were included in anti-EGFR analysis; 3 studies were included in anti-PARP/DNA repair analysis
- 3 trials were included in miscellaneous analysis); 27 were eligible for PFS analysis (among them, we underlined, that: 13 were included in anti-angiogenetic analysis; 4 studies were included in anti-EGFR analysis; 2 studies were included in anti-PARP/DNA repair; 8 trials were included in miscellaneous analysis)

Qualität der Studien:

- Twenty trials were scored A (low risk of bias), 9 trials was scored B (intermediate risk of bias), and 1 trial was scored C (high risk of bias)

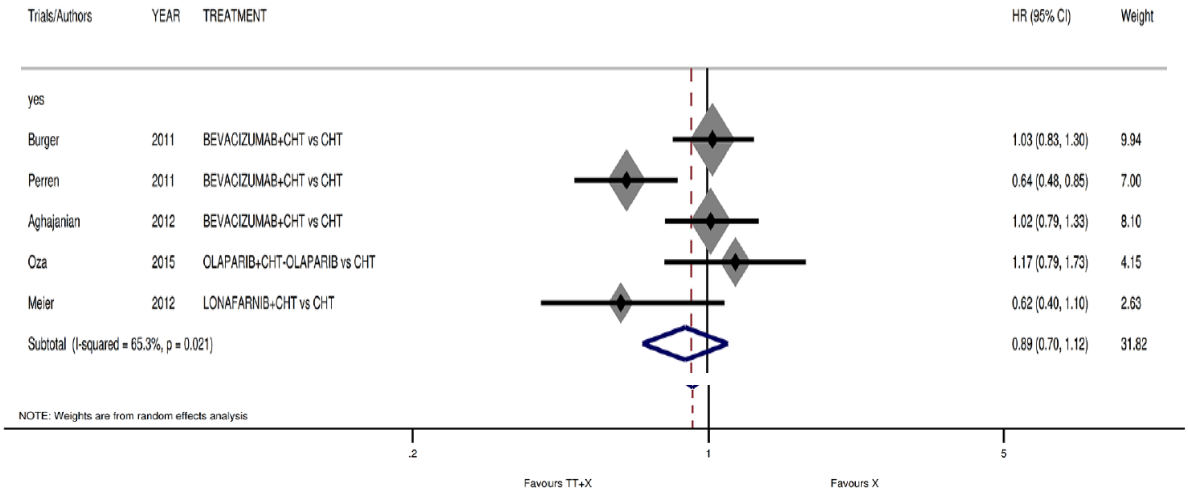
Studienergebnisse:

OS

- Eleven trials were excluded from OS analysis because of missing data.
- Our OS analysis showed that targeted therapy *plus* conventional therapy produced a statistically significant, but marginal benefit in EOC patients compared to conventional therapy alone (pooled HR 0.915; 95%CI 0.840-0.997; *p*=0.043)
- We reported a subgroup analysis on target-therapy pathway.
  - In particular, a significant benefit for anti-angiogenetic agents only, in terms of OS (HR 0.872; 95%CI 0.761-1.000; *p*=0.049), was demonstrated
  - We performed a single meta-analysis considering 3 subgroups: platinum-status, line of treatment and maintenance without evidence of significant differences in the subgroups for each analysis (= No statistically significant difference)

Comparison of OS according to maintenance phase

Subtotal: HR [95% CI]: 0,89 [0,70; 1,12] (I2: 65,3%)

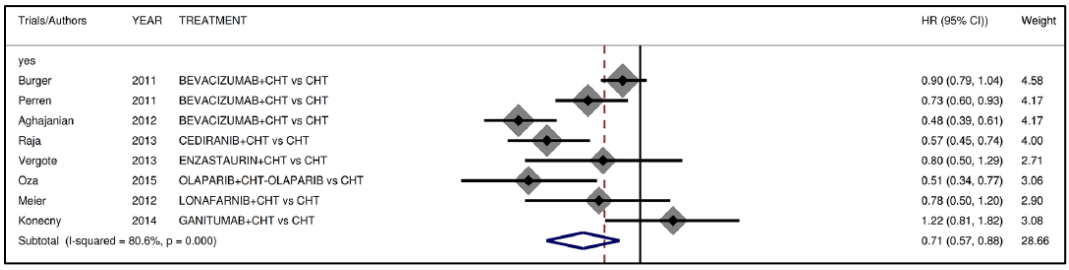


PFS

- Three trials were excluded from PFS analysis because of missing data.
- By our PFS analysis targeted therapy-based treatment demonstrated a significant benefit compared to a conventional treatment (pooled HR 0.807; 95%CI 0.717-0.907; p<0.001). In more detail, we showed a significant benefit for anti-angiogenetic agents only, in terms of PFS (HR 0.740; 95%CI 0.628- 0.872; p<0.001). Moreover, we reported a significant advantage in subgroup analysis in relation to the line of treatment (HR 0.792 in second line versus 0.860 in first line; p=0.004 versus 0.006, respectively)

Comparison of PFS according to maintenance phase.

- subgroup with a maintenance (post-combination) phase, we reported a limited but statistically significant benefit in studies with or without maintenance (HR 0.709 [0,57; 0,88] in maintenance group versus 0.850 in no maintenance group; p=0.002 versus 0.021, respectively)



Anmerkung/Fazit der Autoren

This systematic review and meta-analysis provide the first evidence that targeted therapy is potentially able to translate into improved survival of EOC patients, with a major role played by anti-angiogenetic drugs.

Hinweise

- different studies with partly non-approved drugs and different therapy lines, no results for therapy lines > 2

Staropoli N et al., 2018 [17].

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

- We confirm the significant benefit in terms of PFS compared to control arm. In particular, we dwell attention on sensitivity analyses and each one of subgroup. 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.

Qian X et al., 2015 [13].

Maintenance Therapy in Ovarian Cancer with Targeted Agents Improves PFS and OS: A Systematic Review and Meta-Analysis

Fragestellung

comprehensive metaanalysis was conducted to provide a reference of clinical options on the use of maintenance therapy with targeted agents to treat patients with ovarian cancer

Methodik

Population:

- patients with a definite diagnosis of ovarian cancer, and (2) who had previously received adjunctive treatments such as cytoreductive surgery and standard chemotherapy

Intervention:

- targeted maintenance therapy after standard treatment

Komparator:

- placebo or who were only observed following standard chemotherapy

Endpunkte:

- PFS, OS, Safety

Recherche/Suchzeitraum:

- to January 2015

Qualitätsbewertung der Studien:

- Cochrane Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

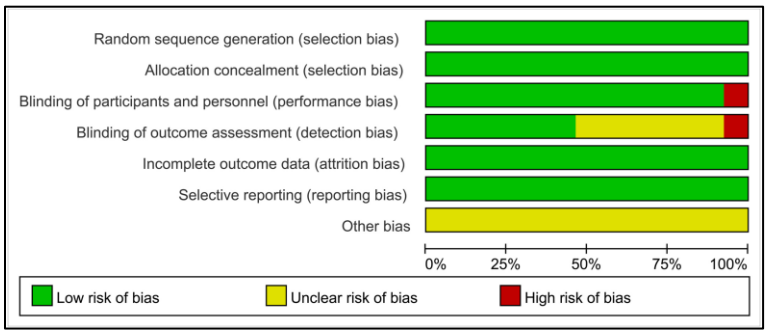
- 13 studies (n=5578)
- 3010 patients were treated with maintenance therapy using targeted agents, and the remaining 2568 patients were treated with placebo (except for one patient in a control group, who was only subjected to observation after receiving standard chemotherapy)

Charakteristika der Population:

Table 1. Characteristics of included trials.

Study	Year	Country	Recruitment period	Drug	RCT phase	Patients number		Age (year)		Survival outcome
						Targeted	Control	Targeted	Control	
Berek	2009	USA	2002–2007	Oregovomab	III	251	120	58.8	59.6	PFS
Bois	2014	Germany	2009–2014	Pazopanib	III	472	468	56	57	OS,PFS
Burger	2011	USA	2005–2009	Bevacizumab	III	623	625	60	60	OS,PFS
Herzog	2013	USA	2008–2009	Sorafenib	II	123	123	56.9	54.4	PFS
Hirte	2006	Canada	1998–1999	BAY 12–9566	III	122	121	58.4	56.7	OS
Karlan	2012	USA	2007–2009	AMG 386	II	53	55	59	62	OS,PFS
Kaye	2012	USA	2008–2009	Vismodegib	II	52	52	57.3	58.6	PFS
Ledermann	2011	UK	2006–2008	Nintedanib	II	43	40	58.4	61.3	OS,PFS
Ledermann	2012	UK	2008–2010	Olapanib	II	136	129	58	59	OS,PFS
Meier	2012	Germany	2006.2–2006.9	Lonafarnib	II	53	52	61	56	OS,PFS
Sabbatini	2013	USA	2006–2009	Abagovomab	III	593	295	56.3	56	OS,PFS
Vergote	2013	Belgium	2006–2012	Enzastaurin	II	69	73	53.6	54.5	PFS
Vergote	2014	Belgium	2005–2008	Erlotinib	III	420	415	59	59	OS,PFS

Qualität der Studien:



Studienergebnisse:

- **PFS**
  - Almost all of the included trials (12/13) [8, 9, 12–15, 18, 20–22, 24, 25] considered PFS as the primary end point and OS or trial termination as the secondary end point. All 12 trials provided HR values regarding PFS. Here, we chose a randomeffects model because of the differences that were observed between the above discussed trial groups ($p < 0.0001$ and $I2 = 94\%$). By sensitivity analyses, we excluded the trial by Ledermann for high heterogeneity [8]. Then the heterogeneity among the left 11 trials as measured by PFS changed to an acceptable level ($I2 = 66\%$). Targeted maintenance therapy was found to significantly improve PFS when compared to placebo groups (HR = 0.84, 95%CI: 0.75 to 0.95, $p = 0.001$).
- **OS**
  - Overall survival (OS). A total of 9 trials [8, 9, 12–14, 19, 20, 22, 25] provided HR values about OS. We chose a fixed-effect model to evaluate the differences between the above trials ($p = 0.07$ and $I2 = 45\%$). Maintenance therapy with targeted agents was found to be associated with significant improvements in OS when compared to placebo groups (HR = 0.91, 95%CI: 0.84 to 0.98, $p = 0.02$).
- **Safety (adverse events)**
  - Generally, level 3/4 grade adverse events (according to CTCAE: Common Terminology Criteria for Adverse Events) are considered to affect quality of life [18, 22]. Therefore, we assessed the quality of life in the patients that experienced level 3/4 adverse events.
  - adverse events that were reported in more than 5 of the trials were defined as abdominal pain, fatigue, diarrhea, nausea, constipation, vomiting, hypertension, and joint pain. Pool OR values suggested that maintenance therapy using targeted agents significantly increased the incidence of fatigue (OR = 2.72, 95%CI: 1.44 to 13, $p = 0.002$), diarrhea (OR = 4.77, 95%CI: 2.68 to 8.48, $p < 0.001$), nausea (OR = 3.63, 95%CI: 1.09 to 12.03, $p = 0.04$), vomiting (OR = 2.86, 95%CI: 1.07 to 7.68, $p = 0.04$), hypertension (OR = 4.44, 95%CI: 3.16 to 6.22, $p < 0.001$) but did not markedly increase the incidence of abdominal pain (OR = 1.10, 95%CI: 0.69 to 1.76, $p = 0.42$), constipation (OR = 0.69, 95%CI: 0.22 to 2.15, $p = 0.53$) or joint pain (OR = 0.97, 95%CI: 0.30 to 3.18, $p = 0.96$). Overall, the risk of withdrawal of treatment as a result of adverse events was significantly increased in the targeted maintenance therapy groups when compared to the placebo groups (OR = 4.08, 95%CI: 1.92 to 8.68, $p < 0.001$ and $I2 = 86\%$).

- The obvious heterogeneity might be related to the prevention of risks, benefits, and financial costs. The conclusion assessing withdrawal of treatment should be used cautiously.

Subgroup-analyses

- In 2 trials, standard chemotherapy was combined with targeted agents as the first-line therapy, whereas in the remaining 11 trials the first-line therapy was standard chemotherapy only. There were no significant differences in therapeutic effectiveness (PFS, OS) between subgroups.
- There were also no significant differences between subgroups according to which targeted agents were employed (monoclonal antibody vs. small molecules).
- Finally, 2 subgroups were divided according to the withdrawal rate (>30% vs. <30%) of targeted maintenance therapy, and the results indicated that there were significant differences among them.
- One of the subgroups was insufficiently studied, which reduces the credibility of the results that were obtained in the above subgroup analyses.

Anmerkung/Fazit der Autoren

In conclusion, the results of our meta-analysis suggested that maintenance therapy with targeted agents may not only postpone the progress of ovarian cancer but may also improve survival.

However, this treatment approach also increases the incidence of adverse events that are related to ovarian cancer. In our opinion, the above discussed pros and cons must be weighed with respect to the clinical application of using targeted maintenance therapy in ovarian cancer patients. Additional multi-center RCTs with larger patient cohorts should be required before maintenance therapy with targeted agents becomes a widely used clinical choice for the treatment of ovarian cancer.

Guo XX et al., 2018 [7].

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

<u>Population:</u>

- cancer patients

<u>Intervention/ Komparator:</u>

- 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).

Ovarian Cancer

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.

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:

Only subgroup analyses for ovarian cancer will be reported

- **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)

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.

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2019 [9].

DGGG, DKG, Deutsche Krebshilfe, AWMF

S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren, Version 3.0 – January 2019, AWMF-Registernummer: 032-035OL

siehe auch: Leitlinienprogramm Onkologie, 2019 [8].

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: ca. 3 Jahre

Recherche/Suchzeitraum:

- Recherche für Version 2.1. Aktualisierungsrecherchen von 1.3.2016 – 30.06.2017; auf RCT beschränkt; Version 2.: Recherche von Primärstudien bis 03.2016; Version 1: Leitlinienadaptionen und syst. Literaturrecherche bis 2010

Änderungen bzw. Neuerungen in der Version 2.1.

- Die Aktualisierung der Leitlinie zwischen 2017 und 2018 führten zu einigen relevanten Änderungen. Neue Studienergebnisse führten in den Bereichen Vorläuferformen des Ovarialkarzinoms, genetische Beratung, molekularpathologische Marker, Kombinations-Chemotherapieregime, HIPEC, Einsatz von PARP-Inhibitoren und Keimstrang-Stromatumoren zu geänderten 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 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

8.9.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad **A**	Erhaltungs-/Konsolidierungstherapien nach Abschluss der Primärtherapie sollen nicht durchgeführt werden*. *Für die Wirksamkeit einer Konsolidierungs- oder Erhaltungstherapie im Hinblick auf PFS liegen nur Daten für Antiangiogenetische Therapien vor (siehe 8.6.)	
Level of Evidence **1+**	Primärstudien: [380, 381, 408-415]	

Eine Erhaltungs- bzw. Konsolidierungstherapie beschreibt die Therapie über die klinische, radiologische oder serologische Komplettremission hinaus bzw. über die Applikation von 6 Zyklen Carboplatin/Paclitaxel hinaus. Diese wurde sowohl für zytostatische Therapie (z. B. Paclitaxel-Erhaltungstherapie) als auch z. B. Strahlentherapie in Studien untersucht, ohne dass ein reproduzierbarer Vorteil hinsichtlich des progressionsfreien Überlebens oder Gesamtüberlebens der Patientinnen beobachtet werden konnte [380, 381, 408-415].

Einzig für die Wirksamkeit einer Erhaltungs- bzw. Konsolidierungstherapie mit Bevacizumab liegen Daten in Hinblick auf eine Verlängerung des progressionsfreien Überlebens vor.

380. Burger, R.A., et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med, 2011. 365(26): p. 2473-83.

381. Perren, T.J., et al., A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med, 2011. 365(26): p. 2484-96.

408. Lambert, H.E., et al., A randomized trial of five versus eight courses of cisplatin or carboplatin in advanced epithelial ovarian carcinoma. A North Thames Ovary Group Study. Ann Oncol, 1997. 8(4): p. 327-33.
409. Sorbe, B., et al., Chemotherapy vs radiotherapy as consolidation treatment of ovarian carcinoma stage III at surgical complete remission from induction chemotherapy. ASCO, 1996.
410. Mei, L., et al., *Maintenance chemotherapy for ovarian cancer.* Cochrane Database Syst Rev, 2010(9): p. CD007414.
411. Berek, J., et al., Oregovomab maintenance monoimmunotherapy does not improve Enpunkte in advanced ovarian cancer. J Clin Oncol, 2009. 27(3): p. 418-25.
412. Pecorelli, S., et al., Phase III trial of observation versus six courses of paclitaxel in patients with advanced epithelial ovarian cancer in complete response after six courses of paclitaxel/platinum-based chemotherapy: final results of the After-6 protocol 1. J Clin Oncol, 2009. 27(28): p. 4642-8.
413. Penson, R.T., et al., Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors. J Clin Oncol, 2010. 28(1): p. 154-9.
414. Pomel, C., et al., Hyperthermic intra-peritoneal chemotherapy using oxaliplatin as consolidation therapy for advanced epithelial ovarian carcinoma. Results of a phase II prospective multicentre trial. CHIPOVAC study. Eur J Surg Oncol, 2010. 36(6): p. 589-93.
415. Hess, L.M., et al., Continued chemotherapy after complete response to primary therapy among women with advanced ovarian cancer: a meta-analysis. Cancer, 2010. 116(22): p. 5251-60.

Systemische Rezidivtherapie

9.2.1.	Rezidivtherapie, wenn eine Platin-haltige-Therapie keine Option ist (platin-resistentes Rezidiv)	
9.2.	Evidenzbasiertes Statement	geprüft 2018
Level of Evidence 1+	Eine Kombinationschemotherapie bietet keinen Vorteil gegenüber einer Monotherapie.	
	Leitlinien: NHS TA91 [366] Primärstudien: [434, 435, 437, 444-451]	
9.3.	Evidenzbasiertes Statement	geprüft 2018
Level of Evidence 1+	Endokrine Therapien sind einer Monochemotherapie unterlegen.	
	Leitlinien: NHS TA91 [366] Primärstudien: [434, 435, 437, 444-451]	
9.4.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Patientinnen mit platinresistentem und/oder -refraktärem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine nicht platinhaltige Monotherapie erhalten. Folgende Zytostatika können in Betracht gezogen werden: • Pegyliertes liposomales Doxorubicin, • Topotecan, • Gemcitabin, • Paclitaxel wöchentlich.	
Level of Evidence 1+	Leitlinien: NHS TA91 [366] Primärstudien: [434, 435, 437, 444-451]	

9.5.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad 0	Bevacizumab kann in Kombination mit Paclitaxel, Topotecan oder pegyliertem liposomalen Doxorubicin zur Behandlung von Patientinnen mit platinresistentem Rezidiv angewendet werden.	
Level of Evidence 1+	Primärstudien: [452]	

Beim platinresistenten Rezidiv (Rezidiv innerhalb von 6 Monaten nach Abschluss der Primärtherapie) eines Ovarialkarzinoms wird die Durchführung einer nicht platinhaltigen Monochemotherapie empfohlen. Eine gegenüber anderen Therapien überlegene Aktivität wurde für Topotecan und pegyliertes liposomales Doxorubicin in randomisierten Studien gezeigt [437]. Bei taxannaiven Patientinnen zeigen Topotecan und Paclitaxel ähnliche Wirksamkeit [435, 445]. Gemcitabin wurde in 2 Studien im Vergleich zu pegyliertem liposomalem Doxorubicin untersucht. Beide Studien waren als Überlegenheits-Studien gegenüber pegyliertem liposomalem Doxorubcin geplant und verfehlten ihren primären Endpunkt, beide Substanzen scheinen jedoch ähnlich aktiv zu sein [447, 448]. Eine Alkylantientherapie mit Treosulfan oder Canfosfamide war einer Therapie mit Topotecan bzw. pegyliertem liposomalem Doxorubicin unterlegen [444, 453]. Bisher konnte kein Effektivitätsvorteil für eine Kombinationschemotherapie bei platinresistentem Rezidiv aufgezeigt werden [450].

Chemotherapien sind effektiver als endokrine Therapien. Dies gilt z. B. für die Vergleiche von Treosulfan mit Leuprorelin, sowie Tamoxifen mit pegyliertem liposomalem Doxorubicin oder Paclitaxel [434, 435, 437, 444-450, 454] [455]. Es gibt Hinweise auf eine Verlängerung des progressionsfreien Intervalls durch die Addition von Bevacizumab zu einer Chemotherapie mit pegyliertem liposomalen Doxorubicin, Topotecan oder Paclitaxel [456]. Die Kombination sollte nur bei Patientinnen zum Einsatz kommen, die zuvor keine VEGF-gerichtete Therapie erhalten haben. Gerade der Effekt auf das Sistieren der Ascitesbildung kann jedoch einen wiederholten Einsatz sinnvoll machen, was jedoch einem off-label entsprechen würde. Dem Therapieziel „Optimierung der Lebensqualität“ kommt in der platinresistenten Situation besondere Bedeutung zu [457].

366. NHS National Institute for Health and Clinical Excellence. Technology Appraisal Guidance 91 Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. 2005 [cited 2012 September 7]; Available from: http://www.nice.org.uk/TA091.
434. Williams, C., I. Simera, and A. Bryant, Tamoxifen for relapse of ovarian cancer. Cochrane Database Syst Rev, 2010(3): p. CD001034.
435. ten Bokkel Huinink, W., et al., Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol, 1997. 15(6): p. 2183-93.
437. Gordon, A.N., et al., Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol, 2001. 19(14): p. 3312-22.
444. Meier, W., et al., Topotecan versus treosulfan, an alkylating agent, in patients with epithelial ovarian cancer and relapse within 12 months following 1st-line platinum/paclitaxel chemotherapy. A prospectively randomized phase III trial by the Arbeitsgemeinschaft
Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). Gynecol Oncol, 2009. 114(2): p. 199-205.
445. ten Bokkel Huinink, W., S.R. Lane, and G.A. Ross, Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. Ann Oncol, 2004. 15(1): p. 100-3.
446. Vergote, I., et al., Phase 3 randomised study of canfosfamide (Telcyta, TLK286) versus pegylated liposomal doxorubicin or topotecan as third-line therapy in patients with platinum-refractory or -resistant ovarian cancer. 2009(1879-0852 (Electronic)).
447. Ferrandina, G., et al., Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol, 2008. 26(6): p. 890-6.
448. Mutch, D.G., et al., Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. 2007(1527-7755 (Electronic)).
449. du Bois, A., et al., Chemotherapy versus hormonal treatment in platinum- and paclitaxel-refractory ovarian cancer: a randomised trial of the German Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Study Group Ovarian Cancer. 2002(0923-7534 (Print)).
450. Sehouli, J., et al., Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol, 2008. 26(19): p. 3176-82.
451. Peng, L.H., X.Y. Chen, and T.X. Wu, Topotecan for ovarian cancer. 2008(1469-493X (Electronic)).
452. Pujade-Lauraine, E., et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol, 2014. 32(13): p. 1302-8.
457. Friedlander, M., et al., Symptom control in patients with recurrent ovarian cancer: measuring the benefit of palliative chemotherapy in women with platinum refractory/resistant ovarian cancer. Int J Gynecol Cancer, 2009. 19 Suppl 2: p. S44-8.

9.2.2. Rezidivtherapie basierend auf einer erneuten platin-haltigen Therapie (platin-sensitives Rezidiv)

9.6.	Konsensbasierte Empfehlung	modifiziert 2018
EK	Patientinnen mit platinsensitivem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine platinhaltige Kombinationstherapie erhalten. Folgende Kombinationen können in Betracht gezogen werden*: • 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 [458, 459]. 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 [436] und Carboplatin/Gemcitabin [460] 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 [461].

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 [462]

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 [463]. In dieser Subgruppe konnte bisher allerdings keine Überlegenheit einer Nicht-Platinhaltigen Therapie (pegyliertes liposomales Doxorubicin) im Vergleich zu einer platinhaltigen Therapie aufgezeigt werden [464]. Somit ist auch in dieser Subpopulation der Standard eine platinbasierte Therapie. Der direkte Vergleich zwischen platinbasierter Kombination versus Trabectedin mit peglyiertem liposomalen Doxorubicin wurde in der Inovatyon-Studie untersucht. Die Ergebnisse sind noch ausstehend.

458. 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.
459. 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.
460. 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.
461. 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.
462. 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.
463. Monk, B.J., et al., Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. J Clin Oncol, 2010. **28**(19): p. 3107-14.
464. 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: p. JCO2017734293.

9.3. Operative Rezidivtherapie

9.7.	Evidenzbasiertes Statement	geprüft 2018
Level of Evidence 2+	Der Stellenwert der Rezidivchirurgie beim Ovarialkarzinom lässt sich nicht durch prospektive Studiendaten mit hohem Evidenzniveau belegen, retrospektive Daten sprechen für einen möglichen klinischen Nutzen.	
	Leitlinien: SIGN [4] Primärstudien: [465-470]	

9.8.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad B	Ziel der Rezidivoperation sollte die makroskopische Komplettresektion sein.	
Level of Evidence 2+	Leitlinien: SIGN [4] Primärstudien: [465-470]	

Der Stellenwert der Rezidivoperation wird prospektiv in der randomisierten AGO-OVAR OP.4 (DESKTOP 3)-Studie untersucht. Es zeigte sich hier ein signifikanter Unterschied im PFS zugunsten der Rezidivoperation gefolgt von einer Systemtherapie versus einer alleinigen Systemtherapie. Der primäre Endpunkt der Studie (Gesamtüberleben) ist noch ausstehend. Es scheinen nur Patientinnen mit platinsensitivem Rezidiv, die im Rahmen der Rezidivoperation tumorfrei operiert werden können, von diesem Ansatz zu profitieren [467-469, 471, 472] [473]. Als prädiktiv günstige Parameter für das Erzielen der Tumorfreiheit wurden ein guter Allgemeinzustand, Tumorfreiheit nach Primäroperation und kein Nachweis von Aszites beim Rezidiv validiert (AGO-Score) [470]. Demzufolge kann Patientinnen mit platinsensitivem Ovarialkarzinomrezidiv (therapiefreies Intervall > 6 Monate), bei denen Tumorfreiheit erreichbar scheint, die Rezidivoperation angeboten werden. Es gibt keine Daten, die eine Prognoseverbesserung durch eine Rezidivoperation bei platinresistentem Ovarialkarzinomrezidiv aufzeigen.

465. Eisenkop, S.M., R.L. Friedman, and N.M. Spirtos, The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. 2000(0008-543X (Print)).
466. Harter, P., et al., Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. 2006(1068-9265 (Print)).
467. Sehouli, J., et al., Role of secondary cytoreductive surgery in ovarian cancer relapse: who will benefit? A systematic analysis of 240 consecutive patients. J Surg Oncol, 2010. **102**(6): p. 656-62.
468. Galaal, K., et al., Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer. Cochrane Database Syst Rev, 2010(6): p. CD007822.
469. Bristow, R.E., I. Puri, and D.S. Chi, *Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis.* Gynecol Oncol, 2009. **112**(1): p. 265-74.
470. Harter, P., et al., Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer, 2011. **21**(2): p. 289-95.

9.4. Therapie mit PARP-Inhibitoren

9.9.	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad 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 1+	Primärstudien: [474-481]	

9.10.	Evidenzbasierte Empfehlung	neu 2018
Empfehlungsgrad 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. *Zugelassen ist Rucaparib (Stand 19/2018)	
Level of Evidence 2+	Primärstudien: [474-481]	

Patientinnen mit einem high-grade Ovarialkarzinomrezidiv, die auf eine platinhaltige Chemotherapie angesprochen haben, kann eine Erhaltungstherapie mit Niraparib (300mg/d) und Olaparib (Tabletten 600mg/d) angeboten werden. Die Entscheidung zwischen beiden Medikamenten sollte nach Erwägung des Nebenwirkungsprofils und der Patientinnenpräferenz erfolgen, da direkt vergleichende Studien zur Wirksamkeit und dem Nebenwirkungsprofil fehlen.

Niraparib

Die Effektivität von Niraparib wurde in der randomisierten, doppelblinden, placebokontrollierten Phase-3-AGO-OVAR-2.22/ENGOT-OV16/NOVA-Studie (NCT01847274) als Erhaltungstherapie nach erfolgreicher (mindestens Partialremission) platinbasierter Chemotherapie untersucht [479]. Die Patientinnen wurden in zwei Gruppen unterteilt (positiv oder negativ für eine BRCA-Keimbahnmutation: gBRCA bzw. non-gBRCA) und danach 2:1 randomisiert und erhielten bis zum Erkrankungsprogress entweder Niraparib (300mg einmal täglich) oder Placebo. Der primäre Endpunkt war das PFS bei Patientinnen mit high-grade serösem Ovarialkarzinom mit sowohl BRCA-Mutation als auch nicht BRCA-mutierten die mindestens zwei platinhaltigen Therapien erhalten hatten. Der primäre Endpunkt zeigte einen signifikanten Vorteil zugunsten der Niraparib Erhaltungstherapie in beiden Gruppen (PFS Median gBRCA-positiv: 21,0 Monate vs. 5,5 Monate; HR 0,27, 95%CI, 0,17-0,41; gBRCA-negativ: 9,3 Monate vs. 3,9 Monate, HR 0,45, 95% KI 0,35-0,61). Die häufigsten schweren Nebenwirkungen (> Grad 3) unter Niraparib waren Thrombozytopenie (33,8 % vs. 0,6 %) und Anämie (25 % vs. 0%) [479].

Olaparib

Die Effektivität von Olaparib als Erhaltungstherapie wurde in der Studie 19 überprüft [474-476]. 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) [474]. 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 %) [474]. Für das Gesamtüberleben zeigte sich kein signifikanter Unterschied [476].

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) [480]. 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 [474, 475, 477].

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 [478]. Darüber hinaus wurde im Rahmen der 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 [481].

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Francis J et al., 2017 [3].

Cancer Care Ontario Guideline 4-3 Version 4

Systemic Therapy for Recurrent Epithelial Ovarian Cancer

see also: **Francis J et al., 2017** [4].

Fragestellung:

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

Methodik

Grundlage der Leitlinie:

- TARGET POPULATION
  - The target population comprises women with recurrent epithelial ovarian cancer who have previously received platinum-based chemotherapy. Specific subgroups of interest are identified based on response to therapy.
- INTENDED USERS
  - The intended users of this guideline are gynaecologic oncologists or medical oncologists in the province of Ontario.
- BACKGROUND INFORMATION
  - This guideline was based on an updated systematic review of the 2011 evidence base [1]. New evidence has led to new recommendations in some areas.

THE PROGRAM IN EVIDENCE-BASED CARE

- The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of

Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision-makers from across the province, and methodologists.

- The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (MOHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

- Due to the awareness of new randomized trials on this topic, the CCO PEBC Gynecologic Cancer Disease Site Group (Gyne DSG) chose to update the evidence base and its recommendations for systemic therapy in this patient population.

GUIDELINE DEVELOPERS

- This guideline was developed by the GDG which was convened at the request of the Gyne DSG. The project was led by a small Working Group of the Gyne DSG members, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in gynecologic oncology, medical oncology, and health research methodology. Other members of the Gyne DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

GUIDELINE DEVELOPMENT METHODIK

- The PEBC produces evidence-based and evidence-informed guidance documents using the Methodik of the Practice Guidelines Development Cycle [16,17]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders. The PEBC uses the AGREE II framework [18] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.
- The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development Methodik are described in more detail in the PEBC Handbook and the PEBC Methodik Handbook.

<u>Grundlage der Leitlinie</u>:

- 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.

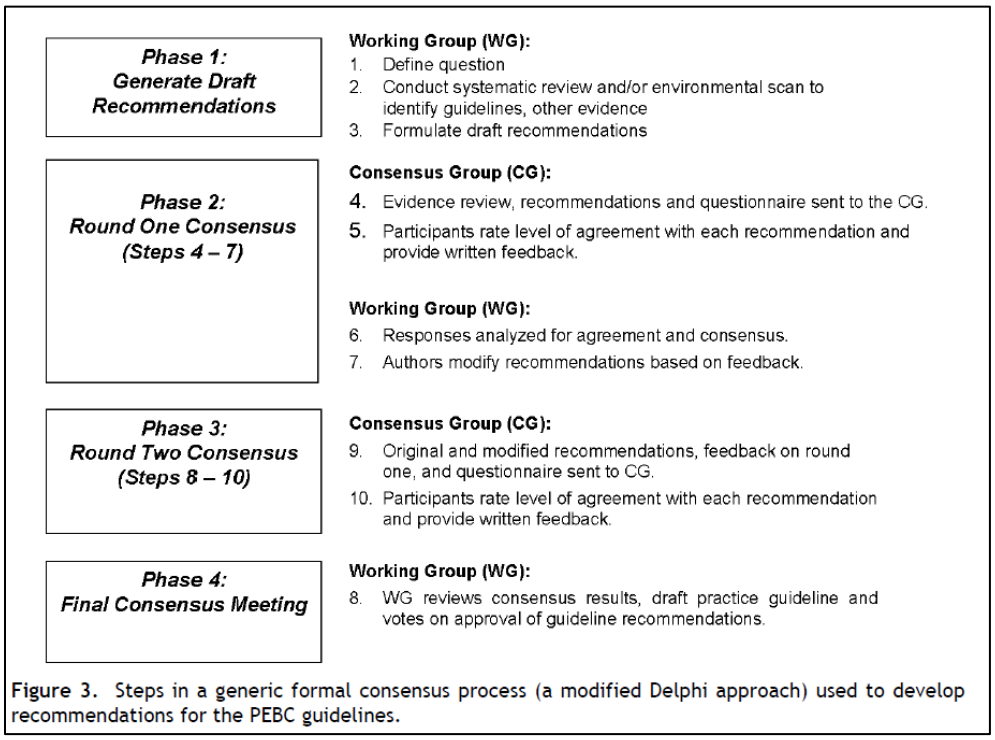

Figure 3. Steps in a generic formal consensus process (a modified Delphi approach) used to develop recommendations for the PEBC guidelines.

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

<u>Chemotherapy for patients with platinum-sensitive recurrent ovarian cancer:</u>
• 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:
  ○ carboplatin and paclitaxel (C-P)
  ○ carboplatin and gemcitabine
  ○ carboplatin and pegylated liposomal doxorubicin (C-PLD)
• 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.
• 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).

Recommendation 5

For patients with platinum-refractory or platinum-resistant recurrent ovarian cancer:

- Lower levels of response to treatment are expected for this group; therefore, the goals of treatment should be to improve patient's QOL by extending the symptom-free interval, reducing symptom intensity, increasing PFS, or if possible, prolonging life.
- Monotherapy with a non-platinum agent should be considered since there does not appear to be an advantage in the use of non-platinum-containing combination chemotherapy in this group of patients. Single-agent paclitaxel, topotecan, PLD, and gemcitabine have demonstrated activity in this patient population and are reasonable treatment options.
- There is no evidence to support or refute the use of more than one line of

chemotherapy in patients with platinum-refractory or platinum-resistant recurrences. There are many treatment options that have shown modest response rates but their benefit over best supportive care has not been studied in clinical trials.

- Bevacizumab combined with chemotherapy (PLD, weekly paclitaxel, or topotecan) can be considered for women who meet the eligibility criteria of the Avastin Use in Platinum-Resistant Ovarian Cancer (AURELIA) phase III RCT; confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within six months of completing ≥4 cycles of platinum-based therapy, age ≥18 years, Eastern Cooperative Oncology Group performance status ≤2, and adequate liver, renal, and bone marrow function. Ineligible patients include those who have received >2 prior anticancer regimens or who had refractory disease, patients with a history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction.

Qualifying Statements for Recommendation 5

- At the time of the writing of this guideline there are numerous targeted agents in addition to vascular endothelial growth factor (VEGF) inhibitors, programmed death-1 (PD1) and programmed death ligand-1 inhibitors (PDL1), as well as other immunotherapies that are under investigation and that show promise in early trials. It is likely that one or some of these will become part of the lexicon of treatment protocols in the near future, either independently or in combination with conventional chemotherapy.

Key Evidence for Recommendation 5

- Based on moderate quality of evidence, in the AURELIA phase III RCT, in women with platinum-resistant recurrent ovarian cancer, the PFS HR was 0.48 (95% CI, 0.38 to 0.60) for chemotherapy including PLD, weekly paclitaxel or topotecan with bevacizumab (BEV+CT) compared with the same regimen although without bevacizumab (CT). Median PFS was 6.7 months in the BEV+CT arm vs. 3.4 months in the CT arm [15].
- Statistically significant increased risks for BEV+CT vs. CT were shown for the following adverse events:
  - Grade ≥2 adverse events including hypertension, gastrointestinal perforation and fistula/abscess: RR, 3.71; 95% CI, 2.03 to 6.78) [15].
  - Grade ≥3 adverse events including hypertension, proteinuria, gastrointestinal perforation, bleeding, thromboembolic event, wound healing, reversible posterior leukoencephalopathy syndrome, congestive heart failure, and cardiac disorders: RR, 2.64; 95% CI, 1.44 to 4.84) [15].
- Based on very low quality of evidence, statistically significant improvements of ≥15% in abdominal/gastrointestinal symptoms were shown for BEV+CT vs. CT (RR, 2.33; 95% CI, 1.37 to 3.97) [15].

Interpretation of Evidence for Recommendation 5

- Based on moderate-quality evidence for PFS, there was a beneficial effect of BEV+CT.
- The above-listed recommendation is conditional in nature (i.e., "can be considered") due to the detection of adverse events with the use of BEV+CT. Although based on low quality of evidence, we do accept lower-tiered evidence to inform harms outcomes, thereby tempering the recommendations despite evidence for improved PFS.

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Suh DH et al., 2018 [18].

Practice guidelines for management of ovarian cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement

Fragestellung:

The objective of these practice guidelines is to establish standard strategies in daily practice of ovarian cancer patients based on the results of the recent publications as well as the consensus of experts as a KSGO Consensus Statement.

Questions:

1. Does systemic PLND and/or PALND improve survival Enpunkte for patients with early-stage EOC apparently confined to an ovary?
2. Are survival Enpunkte from NAC followed by interval cytoreductive surgery vs. primary cytoreductive surgery comparable in patients with extensive stage IIIC-IV EOC who are not likely for optimal cytoreduction?
3. **Does weekly dose-dense paclitaxel regimen improve survival Enpunkte in patients with advanced EOC compared with standard therapy given every 3 weeks?**
4. **Does bevacizumab improve survival Enpunkte in patients with EOC as postoperative first-line therapy or second-line therapy for recurrence?**
5. Is ROMA superior to serum CA125 for differential diagnosis of adnexal tumors in terms of sensitivity and specificity?
6. Does complete staging operation improve survival Enpunkte in patients with serous borderline epithelial ovarian tumors?
7. Does fertility-sparing surgery have negative impact on survival Enpunkte in young patients with early-stage EOC who desire to maintain their fertility?

8. Does PARP inhibitor maintenance therapy improve survival Enpunkte in patients with BRCA-associated EOC?

Methodik

Grundlage der Leitlinie:

Methodik are the same with those of practice guidelines for management of uterine corpus cancer [4] and cervical cancer [5]. Since the last version (V2.0) of the KSGO practice guidelines for gynecologic cancer management in 2010, the Guidelines Revision Committee of KSGO convened again in 2015 to revise V2.0 and make V3.0. In the committee, a comprehensive method for systematic review of relevant literature between 2010 and 2015 was adopted in order to adhere to the principles of evidence-based medicine. The process was as followed: 1) selection of key questions; 2) searching for relevant literature published after 2010 for each key question; 3) determining the level of evidence and grade of recommendation; 4) deduction of the agreements; and 5) review and approval. Key questions were chosen and edited by ovarian cancer sub-committee members considering previous ones in V2.0, the need for further clarification, and new reports after V2.0. Data and literature published between 2010 and 2015 were searched using 3 searching engines: Cochrane Library CENRAL, MEDLINE, and Embase. Then, a meta-analysis and systematic review were conducted for determining the level of evidence. Specifically, Cochrane methodology was used for randomized controlled trials, the Newcastle-Ottawa scale for non-random studies, and the quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS-2) for diagnosis research. The level of evidence was decided as one of the 4 categories (high, moderate, low, and very low) using the methodology suggested by the grade group based on the research design, consistency among the research results, immediacy of the research subject and intervention, possibility of publishing bias, and accuracy of the research results.

The grade of recommendation was decided by the methodology suggested by the grade group based on the level of evidence, considering the application subject, hazard and benefit, social, and individual cost of the intervention, and patients' preference. The grade of recommendation was assigned as strong or weak recommendation. The draft form and grades of recommendation were established through mutual consultation among all the members of the revision committee.

After debates in a public hearing with all members of the KSGO and invited representatives of related academic societies, a tentative version of the guidelines was re-evaluated and supplemented. For an internal and external review, the KSGO sent the final version of the guidelines to related organizations, including the Korean Society for Radiation Oncology (KOSRO), Korean Society of Pathologists (KSP), Korean Cancer Study Group (KCSG), Korean Society of Urogenital Radiology (KSUR), Korean Society of Nuclear Medicine (KSNM), Korean Society of Obstetrics and Gynecology (KSOG), and Korean Gynecologic Oncology Group (KGOG). Subsequent to these reviews, there were no objections or requests for revision. Finally, recommendations of the 2 key questions (4 and 8) were reupdated on the basis of high-level evidence that released after a public hearing. Those updated recommendations were added to this manuscript through the consensus between all ovarian cancer sub-committee members of the Guidelines Revision Committee of KSGO.

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

Table 3. Levels of evidence and grades of recommendations	
Definition	
Level of evidence	
A	High-quality evidence
B	Moderate-quality evidence
C	Low-quality evidence
D	Very low-quality evidence
E	No evidence or difficult to analyze
Grade and recommendation strength	
1	Strong recommendation
2	Weak recommendation

Empfehlungen

1. Systemic PLND and/or PALND may be selectively performed for those patients with EOC apparently confined to an ovary under the physician's discretion despite the lack of evidence for survival improvement compared with selective or omitting PLND and/or PALND **(2B).**
2. NAC followed by interval debulking surgery may be considered for patients with extensive stage IIIC–IV EOC who are not likely for optimal cytoreduction by upfront primary surgery based on that overall survival was comparable between these patients **(2A).**
3. Weekly dose-dense paclitaxel is associated with increased hematologic toxicity compared with standard therapy given every 3 weeks. However, weekly regimen can be considered depending on clinical judgment of gynecologic oncologist because this regimen might improve survival **(2B)**.

[KQ 3]	***Does weekly dose-dense paclitaxel regimen improve survival outcomes in patients with advanced EOC compared with standard therapy given every 3 weeks?*** Weekly dose-dense paclitaxel is associated with increased hematologic toxicity compared with standard therapy given every 3 weeks. However, weekly regimen can be considered depending on clinical judgment of gynecologic oncologist because this regimen might improve survival. ***Level of evidence*: B (moderate)** ***Strength of recommendation*: 2 (weak)**

1. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet. Oct 17 2009;374(9698):1331-1338. 22
2. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. The Lancet. Oncology. Apr 2014;15(4):396-405.
3. van der Burg ME, Onstenk W, Boere IA, et al. Long-term results of a randomised phase III trial of weekly versus three-weekly paclitaxel/platinum induction therapy followed by standard or extended three-weekly paclitaxel/platinum in European patients with advanced epithelial ovarian cancer. European journal of cancer. Oct 2014;50(15):2592-2601.

4. Bevacizumab maintenance following initial chemotherapy with paclitaxel/carboplatin/bevacizumab in patients with EOC can be recommended based on

this regimen has been shown to modestly increase PFS (2A). For recurrence therapy, bevacizumab-containing regimens can be recommended for platinum-sensitive recurrent EOC **(2A)** and platinum-resistant recurrent EOC with priority (level 1) based on these regimens have been shown to increase PFS.

[KQ 4]	***Does bevacizumab improve survival outcomes in patients with EOC as postoperative first-line therapy or second-line therapy for recurrence?*** Bevacizumab maintenance following initial chemotherapy with paclitaxel/carboplatin/bevacizumab in patients with EOC can be recommended based on this regimen has been shown to modestly increase PFS **(2A)**. For recurrence therapy, bevacizumab-containing regimens can be recommended for platinum-sensitive recurrent EOC **(2A)** and platinum-resistant recurrent EOC with priority **(level 1)** based on these regimens have been shown to increase PFS. ***Level of evidence*: A (high)** ***Strength of recommendation*: 2 (weak)**

1. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Nov 20 2007;25(33):5165-5171.
2. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *The New England journal of medicine.* Dec 29 2011;365(26):2484-2496.
3. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jun 10 2012;30(17):2039-2045.
4. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 1 2014;32(13):1302-1308.

5. ROMA can be used for differential diagnosis of adnexal tumors under the clinician's discretion based on the results that ROMA might be more sensitive and specific than CA125 alone **(2D).**
6. Evidence level of whether complete staging operation may lead to better survival compared with incomplete staging operation in serous borderline epithelial tumors cannot be appropriately decided **(E).**
7. For young patients who desire to maintain their fertility, a unilateral salpingo-oophorectomy preserving the uterus and contralateral ovary and comprehensive surgical staging may be considered for select unilateral stage I tumors because fertility-sparing surgery does not seem to damage survival Enpunkte **(2D).**
8. **Poly(ADP-ribose) polymerase (PARP) inhibitor (olaparib tablets) for maintenance therapy can be considered for patients with BRCA-associated EOC, particularly for platinum-sensitive recurrent EOC patients with germline BRCA mutation, because PARP inhibitor maintenance therapy can prolong PFS (1D) (for 2018 update, 2A).**

[KQ 8]	***Does PARP inhibitor maintenance therapy improve survival outcomes in patients with BRCA-associated EOC?*** PARP inhibitor (olaparib tablets) for maintenance therapy can be considered for patients with BRCA-associated EOC, particularly for platinum-sensitive recurrent EOC patients with germline BRCA mutation, because PARP inhibitor maintenance therapy can prolong PFS. ***Level of evidence*: D (very low) → A (for 2018 update)** ***Strength of recommendation*: 1 (strong) → 2 (for 2018 update)**

1. 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 Enpunkte by BRCA status in a randomised phase 2 trial. *The Lancet. Oncology.* Jul 2014;15(8):852-861.
2. Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *The Lancet. Oncology.* Jan 2015;16(1):87-97.
3. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jan 20 2015;33(3):244-250.
4. Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. *Gynecologic oncology.* Jun 2015;137(3):386-391.

Scottish Intercollegiate Guidelines Network 2013 [15].

*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.

1. What is the effect of ultra radical versus standard radical surgery on Enpunkte in patients with advanced ovarian cancer?
2. What are the implications for training of gynaecological oncologists and cross-specialty working with surgeons skilled in bowel resection, diaphragmatic stripping, liver mobilisation and upper abdominal surgery if increasing numbers of women in Scotland receive ultra radical cytoreductive surgery and what are the implications for patients who would be expected to have higher morbidity rates and require additional high dependency or intensive care perioperatively?
3. What is the best pathway for assessment and management of patients with a mildly elevated RMI 1 (below the original scoring development threshold of 200) who may have benign disease or early malignancy?
4. Further validation of newer morphological scoring systems that may supersede RMI 1.
5. Which women are most likely to benefit (in terms of survival and quality of life end points) from hormonal therapy and how does it compare to chemotherapy in platinum-resistant disease?
6. What is the optimal duration of therapy with bevacizumab and are there predictive markers of benefit to bevacizumab?
7. What is the optimal chemotherapy regimen for low-grade serous, clear cell and mucinous histological subtypes of ovarian cancer?

Methodik

Grundlage der Leitlinie:

- SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A Guideline Developer's Handbook
- SYSTEMATIC LITERATURE REVIEW; The year range covered was 2003-2012.
- LITERATURE SEARCH FOR PATIENT ISSUES
- RECOMMENDATIONS FOR RESEARCH
- REVIEW AND UPDATING
- This guideline was issued in 2013 and will be considered for review in three years.

SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

1	Introduction	Updated
2	Key recommendations	New
3	Screening and the role of prophylactic salpingo-oophorectomy	Completely revised
4	Diagnosis	Completely revised
5	Surgical management	Completely revised
6	Chemotherapy	Completely revised
7	Follow up	Completely revised
8	Management of malignant bowel obstruction in relapsed disease	Unchanged
9	Provision of information	Completely revised
10	Implementing the guideline	Completely revised
11	The evidence base	New
Annex 1	Key questions addressed in this update	New
Annex 2	Staging carcinoma of the ovary	Unchanged
Annex 3	Classification of ovarian cancer	Completely revised

Sections 7 (clinical trials) and 9 (specialist palliative care) in SIGN 75 have been removed from this version of the guideline because these are generic topics not specific to the management of epithelial ovarian cancer. Information on resource implications of recommendations, previously in Annex 3, is now in section 10.2.

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 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 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 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 Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Hinweise

This guideline updates SIGN 75, published in October 2003, to reflect the most recent evidence.

Empfehlungen

6.2 ADVANCED DISEASE

Ovarian cancer is made up of different histological subtypes: high-grade serous, low-grade serous, endometriod, mucinous, clear cell and carcinosarcoma. The most frequent subtype is high-grade serous carcinoma and hence these make up the vast majority of patients included in clinical trials. The applicability of the findings and conclusions of these trials to the rarer subtypes is difficult to establish as the numbers are generally too small for separate analysis. However, there is emerging evidence that the different subtypes are different diseases with different clinical behaviour and distinct molecular biology. As a result, they will require different treatment strategies but at present there are limited data and no completed phase III randomised control trials in the separate subtypes on which to base separate treatment recommendations. Where evidence exists from retrospective analyses or non-randomised studies, this will be discussed. Where possible, women should be included in ongoing histo-type specific trials.

6.2.1 ROLE OF PLATINUM AGENTS

Meta-analyses show significant benefit for use of platinum.[128,129] | 1++

A **First line chemotherapy treatment of epithelial ovarian cancer should include a platinum agent either in combination or as a single agent, unless specifically contraindicated.**

6.2.2 CHOICE OF PLATINUM AGENTS

The platinum based drugs cisplatin and carboplatin are equally efficacious in the treatment of epithelial ovarian cancer.[128] Carboplatin has a more favourable toxicity profile. The combination of carboplatin and paclitaxel is as efficacious as cisplatin and paclitaxel combination therapy.[130] | 1++

A **Carboplatin is the platinum drug of choice in both single and combination therapy.**

OTHER AGENTS

Two high-quality RCTs support the use of paclitaxel and cisplatin as an efficacious combination for advanced ovarian cancer.[131,132] A further study has suggested that carboplatin can be substituted for cisplatin.[130] | 1++

Although one RCT has shown that single agent cisplatin yielded both equivalent response rates and equivalent overall survival to cisplatin and paclitaxel, this trial is difficult to interpret due to treatment crossover issues.[131] The study recommends the taxane combination on the grounds of reduced toxicity compared to single agent cisplatin. The ICON 3 trial demonstrates equal effectiveness for carboplatin or CAP (cyclophosphamide, doxorubicin and cisplatin) compared with paclitaxel and carboplatin in ovarian cancer.[133] ICON 3 does not imply that paclitaxel has no role in the treatment of ovarian cancer, but it does suggest that the dramatic difference seen in the earlier studies was principally due to the inferiority of the cyclophosphamide and cisplatin control arm. An interpretation of a meta-analysis of all these studies does suggest a slight benefit for the taxane and platinum combination.[133] | 1++ 1+

Five good quality RCTs, including 6,873 patients, have investigated the addition of a third cytotoxic agent to standard therapy with carboplatin and paclitaxel for the first line treatment of advanced ovarian cancer (some studies included stage Ic to IV, but the majority included stage III and IV).[134-138] Agents investigated were doxorubicin, pegylated liposomal doxorubicin, gemcitabine, topotecan, and cisplatin in various schedules. The addition of a third cytotoxic agent to standard therapy with caroplatin and paclitaxel did not improve survival outcomes[138] but did increase toxicity, particularly haematological toxicity, for example, with gemcitabine,[136,138] pegylated liposomal doxorubicin,[136] and with topotecan.[137] | 1++ 1+

A further RCT comparing induction chemotherapy with carboplatin and gemcitabine (GC arm) to carboplatin and paclitaxel (TC arm) showed better overall survival in the carboplatin and paclitaxel arm, however, this difference was not maintained in a multivariate analysis (HR=1.22, 95% CI 0.99 to 1.52, p=0.067).[139] The incidence of grade 3-4 thrombocytopenia was significantly higher in the GC arm compared with the TC arm (n=279, 67.7% in GC arm; n=48, 11.8% in TC arm; p<0.001), and the incidence of grade ≥2 alopecia was significantly higher in the TC arm compared with the GC arm (n=208, 51.0% for TC; n=30, 7.3% for GC; p<0.001). In addition, the incidence of grade ≥2 neuropathy was also significantly higher in the TC arm compared with the GC arm (n=57, 14.0% for TC; n=9, 2.2% for GC; p<0.001). 1++

An RCT comparing carboplatin (AUC 5) and paclitaxel (175 mg/m²) (standard therapy, TC arm) to carboplatin (AUC 5) and pegylated liposomal doxorubicin (30 mg/m²) (experimental, PLD/C arm) showed that the substitution of PLD for paclitaxel was not superior (OS 61.6 *v* 53.2, respectively, HR=0.89, 95% CI 0.72 to 1.12, p=0.32) but did show a different spectrum of toxicity with less neurotoxicity and alopecia but more haematologic adverse effects (grade 3/4 anaemia, 3% TC *v* 10% PLD/C; grade 3/4 thrombocytopenia, 8% TC *v* 16% PLD/C; ≥2 neuropathy, 19% TC *v* 3% PLD/C; grade 2 alopecia, 60% TC *v* 5% PLD/C). Including all grades, diarrhoea was more common with TC and stomatitis and skin toxicity with PLD/C.[140] 1++

A **Paclitaxel is recommended in combination therapy with platinum in the first line post-surgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, peglated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative.**

A **Patients who are unfit for combination therapy should be offered single agent carboplatin.**

A **A third cytotoxic agent should not be added to carboplatin and paclitaxel.**

6.2.4 SCHEDULING

Increasing the dose intensity by increasing the total dose or decreasing the interval between doses is a potential way of increasing the efficacy of chemotherapy. In recurrent, platinum-resistant, ovarian cancer, high response rates with dose-dense platinum containing regimens have been reported in non-randomised studies. Despite this, several studies have shown no benefit and increased toxicity from increasing the dose intensity of platinum therapy in the first line setting.[141-143]

However, one study in a Japanese population receiving first line therapy for advanced ovarian cancer has shown a significant and sustained improvement in progression-free and overall survival with weekly intravenous dose-dense paclitaxel (80 mg/m², 1-h infusion, given on days 1, 8 and 15) plus carboplatin (AUC 6, given on day one of a 21 day cycle), compared with paclitaxel (180 mg/m²; 3-h infusion) plus carboplatin, given on day 1 of a 21 day cycle. Overall survival at three years was 72.1% in the dose-dense arm versus 65.1% in the control arm (HR=0.75, 95% CI 0.57 to 0.98, p=0.03). The difference is maintained at five years (58.6% *v* 51%, HR=0.79, p=0.0448). Median progression-free survival was 28 months versus 17.2 months (unadjusted HR=0.71, 95% CI 0.58 to 0.88, p=0.0015). Neutropenia (92% *v* 88%) and grade 3/4 anaemia (69% *v* 44%, p<0.001) were higher in the dose-dense arm.[144] It is possible that differences in pharmacogenomics will alter the tolerability of the regimen in a Caucasian population and studies are ongoing which will address this. This regimen also has implications for service delivery and for women undergoing treatment as they would need to attend weekly for 18 weeks instead of six visits but an economic analysis has demonstrated that it is a cost-effective treatment.[145] 1++ 1+ 4

There are several ongoing studies that also assess the efficacy of dose-dense paclitaxel (ICON 8, GOG 262, MITO 7). The results of ongoing clinical trials are required in order to establish whether a regimen of carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m² (day 1, 8, 15 q21) should become the standard of care.

B **Carboplatin AUC 6** (day 1 q21) **and paclitaxel 80 mg/m²** (day 1, 8, 15 q21) **may be considered for the treatment of first line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient.**

✓ Where possible, patients receiving treatment with carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m² (day 1, 8, 15 q21) for first line ovarian cancer should be enrolled in ongoing clinical trials in order to establish if this regime should become the standard of care.

BIOLOGICAL THERAPIES

Two RCTs have investigated the benefit of the addition of bevacizumab, a humanised monoclonal antibody, to vascular endothelial growth factor A (VEGF), to carboplatin and paclitaxel.[146,147] The GOG 218 study was a double-blind, placebo-controlled study of 1,873 patients with untreated stage III and IV disease (including 66% with stage IIIc and >1 cm residual disease or stage IV) and randomised between carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles plus bevacizumab 15 mg/kg during cycles 2–6 and placebo during cycles 7–22 or carboplatin and paclitaxel for six cycles plus bevacizumab during cycles 2–22.[146] A limitation of this study was the change of the primary end point from OS to PFS as maintenance of the blinding after progression was not considered acceptable. Therefore, postprogression therapy was not controlled, so many patients crossed over to receive bevacizumab, affecting the integrity of OS data. There was no difference in PFS between the control group and bevacizumab initiation group but there was a statistically significant improvement in PFS for the group who received bevacizumab throughout (median 10.3 *v* 14.1 months, HR=0.717, 95% CI 0.625 to 0.824, p<0.001). 1++

The ICON 7 study included 1,528 women with high-risk stage I-IIa and advanced stage IIb or IV epithelial ovarian cancer (9% had high risk early-stage disease, 70% had stage IIIc or IV ovarian cancer and 30% had stage IIIc >1 cm residual disease or stage IV). Patients were randomised between carboplatin (AUC, 5 or 6) and paclitaxel (175 mg/m^2), given every three weeks for six cycles, or to this regimen plus bevacizumab (7.5 mg/kg), given concurrently every three weeks for five or six cycles and continued for 12 additional cycles or until progression of disease. There was a small but statistically significant improvement in PFS in the whole population (restricted mean at 42 months was 22.4 months without bevacizumab *v* 24.1 months with bevacizumab p=0.04). In the women with stage IIIc and >1 cm residual disease or stage IV, the benefit was greater (PFS, restricted mean, at 42 months of 14.5 months *v* 18.1 months with respective median overall survival of 28.8 and 36.6 months; HR for death in the bevacizumab group of 0.64, 95% CI 0.48 to 0.85, p=0.002). Bevacizumab was associated with significantly higher rates of bleeding (mainly grade 1 mucocutaneous bleeding), hypertension of grade 2 or higher (18% with bevacizumab *v* 2% with standard therapy), thromboembolic events of grade 3 or higher (7% with bevacizumab *v* 3% with standard therapy), and gastrointestinal perforations (occurring in 10 patients in the bevacizumab group *v* three patients in the standard-therapy group). Quality of life scores did not differ between groups in either study.[147] 1++

The addition of bevacizumab during and after chemotherapy, at both 7.5 mg/kg and 15 mg/kg, prolongs PFS and the benefit is greater in women with incompletely resected (>1 cm residual) stage III and IV disease. The benefit varies over time with maximal benefit in the ICON 7 trial at 12 months and in the GOG 218 trial at 15 months, disappearing by 24 months.[146,147] There was no difference in OS in the GOG 218 trial but these data are compromised by postprogression crossover. A 7.8 month median OS benefit was seen in the group of women with incompletely resected (>1 cm residual) stage III and IV disease. The benefit seen in the ICON 7 trial with 7.5 mg/kg for the patients with stage IIIc and >1 cm residual disease or stage IV disease was similar to the benefit seen in the GOG 218 trial with 15 mg/kg suggesting that 7.5 mg/kg is sufficient. The benefit for those with high-risk early disease and stage III disease with residual disease <1 cm was very small. 1++

Further research is required to determine the optimal duration of therapy and to identify predictive markers of benefit from bevacizumab.

Bevacizumab 15mg/kg is accepted for restricted use by the SMC for combination with carboplatin and paclitaxel, for treatment of patients with stage IV disease *(see section 10.4)*. Bevacizumab at the lower dose of 7.5mg/kg is not currently licensed due to concerns about increased toxicity.[148]

Several other biological agents have been assessed in randomised trials for the first-line treatment of ovarian cancer. These include the CA125-specific murine monoclonal antibody, oregovomab,[150] interferon gamma,[151] the farnesyltransferase inhibitor, lonafarnib,[152] and thalidomide,[153] but none has demonstrated a benefit with respect to PFS or OS. Trials of maintenance oral PARP inhibitors following first-line chemotherapy are ongoing (SOLO-1 and PRIMA).

A **Women with stage IV ovarian cancer should be offered bevacizumab in combination with carboplatin and paclitaxel.**

MAINTENANCE THERAPIES

Despite good initial responses to chemotherapy, most women with ovarian cancer will develop relapsed disease. This has led to an interest in maintenance therapy in order to try to delay relapse and/or increase survival.

A systematic review including six RCTs of 902 women included a meta-analysis of four RCTs (n=479) of maintenance chemotherapy after complete response to first line platinum and paclitaxel which showed no benefit to overall survival from topotecan, anthracyclines or platinum.[154] An additional RCT including 296 women with advanced ovarian cancer who had achieved a complete response to first line platinum-paclitaxel chemotherapy, showed a statistically significant benefit to median PFS of eight months (22 compared with 14 months, p=0.006) but no benefit to overall survival when 12 cycles of maintenance paclitaxel (135 mg/m^2, q 21d) compared to three cycles were given following a complete response to primary platinum/paclitaxel (median OS 53 months *v* 48 months, respectively, p=0.34). There was a higher incidence of grade 2 (23% *v* 15%) and 3 (6% *v* 1%) neuropathy, and grade 3 pain (4% *v* 1%) in the 12-cycle treatment arm.[155] In contrast another study of six cycles of paclitaxel (175mg/m^2) after a complete response showed no difference in PFS or OS.[156] 1++

Continued maintenance therapy with bevacizumab following first line carboplatin, paclitaxel and bevacizumab has been shown to delay progression *(see section 6.2.5)* and the use of continued maintenance therapy with other biological agents is under investigation in clinical trials.

A **For advanced ovarian cancer, maintenance cytotoxic chemotherapy should not be given following standard first line chemotherapy.**

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++ 1+

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++

The addition of bevacizumab to paclitaxel and carboplatin; gemcitabine and carboplatin; or bevacizumab with either PLDH, weekly paclitaxel or weekly topotecan, improved PFS (HR 0.53, 95% CI 0.45 to 0.63) and OS (HR 0.87, 95% CI 0.77 to 0.99).[221] Two of the trials included patients with platinum-sensitive ovarian cancer, and the other was in patients with platinum-resistant cancer. Common adverse events reported with bevacizumab use were hypertension, proteinuria, bleeding, wound healing disruption, gastrointestinal perforations, arterial thrombosis events and venous thrombosis events.[221] 1

Bevacizumab is accepted by SMC for restricted use in combination with paclitaxel in patients with platinum-resistant recurrent ovarian cancer who have received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents *(see section 10.4)*. However, SMC does not recommend it for use in combination with carboplatin and paclitaxel, or in combination with carboplatin and gemcitabine in patients with first-recurrence platinum-sensitive ovarian cancer.

A **Women with platinum-sensitive relapsed ovarian cancer should be offered treatment with carboplatin combined with either paclitaxel or pegylated liposomal doxorubicin hydrochloride** (depending on fitness, comorbidity and toxicity experienced with previous treatment)**.**

A **Women with platinum-resistant ovarian cancer should be considered for treatment with paclitaxel or single agent pegylated liposomal doxorubicin hydrochloride** (depending on fitness, comorbidity and patient's wishes)**.**

A **Women with platinum-resistant relapsed ovarian cancer should be offered bevacizumab in combination with paclitaxel.**

Trials of poly (ADP-ribose) polymerase (PARP) inhibitors have shown benefit in lengthening progression-free survival in patients with advanced, recurrent, platinum-sensitive ovarian cancer.[222-224]

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.	

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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British Gynaecological Cancer Society (BGCS) epithelial ovarian/ fallopian tube/primary peritoneal cancer guidelines: recommendations for practice

Fragestellung:

The remit of this guideline is to collate and propose evidence-based guidelines for the management of epithelial ovarian-type cancers (ovary, fallopian tube or peritoneal origin) and borderline tumours. This document covers all epithelial cancers with any histological subtype.

Methodik

Grundlage der Leitlinie:

- Guidelines produced by the RCOG satisfy the basic criteria laid out in the Appraisal of Guidelines for Research and Evaluation in Europe (AGREE) guidelines. The key features of such guidelines are:
  - a multidisciplinary working group
  - a well-described systematic review of the literature
  - graded recommendations with explicit links to the evidence
  - quality control, e.g. input by an independent advisory board or by independent peer review.
- Existing Green-top Guidelines will require review, and update if appropriate, 3 years post publication. An exception to this process will be where a guideline is found to substantially conflict with recently published evidence. In these cases the guideline will be removed and only republished once an update has occurred. This process will effectively follow the same methodology as newly commissioned guidelines. Guideline leads of existing guidance will not be expected to start a revision unless requested by GC.
- Evidence was searched in the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2010, Issue 3), MEDLINE and EMBASE up to August 2014, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.
- Guideline development process:
  - 1. These guidelines are the property of the BGCS and the Society reserves the right to amend/withdraw the guidelines.
  - 2. The guideline development process is detailed below: a) Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic; b) Lead then identified a team called the guideline team (GT) to develop the 1st draft; c) 1st draft was submitted to the GC; d) GC approved draft and recommended changes; e) Changes

were accepted by the GT who produced the guidelines; f) 2nd draft was then submitted to council members and officers; g) Council and officers approved 2nd draft and recommended changes; h) Changes were then accepted by GC and GT; i) 3rd draft was sent to national and international peer review; j) GC and GT then made changes based on peer review comments; k) 4th draft was sent back to council for approval; l) 4th draft was sent to BGCS members for feedback; m) GC and GT then made changes based on members' feedback; n) 5th draft was sent to public consultation including patient support groups; o) GCand GT thenmade changesbased onnon-members' feedback; p) Final draft approved by council and officers.

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

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 of RCTs or RCTs with a low risk of bias
1–	Meta analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2–	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies e.g. case reports, case series
4	Expert opinion

Figure 3: Grades of recommendation

A	At least one meta analyses, systematic reviews or RCT rated as 1++, and directly applicable to the target population; *or* A systematic review of RCTs or 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* 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* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^+

Good Practice Points

✓	Recommended best practice based on the clinical experience of the guideline development group*

**on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated ☑. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.*

Empfehlungen

Management of recurrent disease

Surgical treatment of recurrent disease

- Cytoreductive surgery could be offered to patients with platinum-sensitive ovarian cancer relapse where the disease appears completely resectable in patients with a good performance status, as this has shown to be associated with improved OS and PFS in retrospective studies and meta-analyses; patients should however be aware that the disease will remain chronic, and that no prospective trials have yet proven a survival benefit. (Grade C)
- Palliative surgery for bowel obstruction could be discussed after failure of conservative treatment and after careful consideration of the patient's overall prognosis, quality of life, previous treatments, future therapeutic options and co-morbidities. Iatrogenic induced short bowel syndrome with the necessity of long life total parenteral nutrition should be avoided and plans for surgery should be agreed within a specialist MDT. (Grade C)

The value of surgery for relapsed ovarian cancer on overall survival in patients with EOC has not yet been established in prospectively randomised trials, but when complete tumour removal can be achieved, retrospective studies have shown a significantly longer OS and PFS when compared to women with residual disease following surgery for relapse. This survival benefit persists even in multifocal relapse and peritoneal carcinosis as long as complete

tumour clearance is achieved [97–100]. Carefulconsiderationofcaseswithin aspecialist MDTcanidentify individuals whose disease may benefit from a surgical approach. In a large, retrospective, systematic trial (DESKTOP I), patients with two out of three of complete resection at first surgery, good performance status and absence of ascites, had an improved survival [97]. No RCT- level data were identified in systematic reviews [101,102]. Four prospective multicentre randomised trials evaluating the value of surgery at relapse are now underway: DESKTOP III [NCT01166737] usedthe selection criteria detailed above andis in followup, GOG 213 [NCT00565851] incorporates the addition of bevacizumab to chemotherapy, SOC1 [NCT01611766] from the Shanghai Gynecologic Oncology Group, and the SOCceR from the Netherlands [NTR3337]. The results of these prospective trials will define the value of cytoreductive surgery at relapse. EOC patients often present with symptoms of acute or sub-acute bowel obstruction at relapse, often attributable to diffuse peritoneal dissemination of recurrent tumour rather than a single point of obstruction. The implementation of novel targeted therapies with anti-angiogenic potential may favour fistula formation or intestinal perforation and so recurrent EOC, with the potential to be complicated by such severe and acute events, constitutes a therapeutic dilemma [103]. No RCTs exist comparing surgical and medical management, and evidence that showed a benefit to surgery over octreotide was of low quality [104]. In a retrospective review of 90 patients who underwent surgery for bowel obstruction in relapsed ovarian cancer, the median OS was 90.5 days (range, <1 day-6 years) [105]. Palliative surgery in patients with gastrointestinal and other symptoms of ovarian cancer recurrence therefore requires multidisciplinary consider-ation [100,105]. Any perceived benefits should be carefully balanced against the risks for each individual patient and factors such as co-morbidities, baseline quality of life, previous response to chemotherapy, length of treatment intervals and patient wishes are likely to be crucial. The management of these cases should be led by specialist gynaecological multidisciplinary teams, including palliative care input at an early stage. If surgery is planned, intra-operative input from gynaecological oncologists is important, so that likelihood of chemotherapy responses after palliative surgery is considered when making intra-operative decisions. Endoscopic techniques, such as placement of intestinal stents and percutaneous endoscopic gastrostomy (PEG), may allow the palliation of gastrointestinal symptoms with reduced procedure- related morbidity in selected patients. Surgical intervention should be restricted to cases where there is a distal mechanical bowel obstruction and where the formation of a proximal high output small bowel stoma is not likely to be necessary, as such high output stomas significantly reduce quality of life and require permanent total parenteral nutrition (TPN). Pre-operative imaging demonstrating the most proximal point of bowel obstruction should be used to identify patients with a level of obstruction at high risk of iatrogenic short bowel syndrome. Management of patients with bowel obstruction should ideally happen within multi-disciplinary teams with experience in managing such cases [106].

Systemic treatment of recurrent disease

- In patients with longer treatment free intervals (TFI) (>6 months), combination therapies with platinum re-challenge are recommended. (Grade A)
- In patients with short TFIs (<6months) single agent therapy is equally effective and less toxic than combination therapies. (Grade A)

Along with patient factors, including patient choice and performance status, residual toxicities and prior hypersensitivity reactions, the most important factors that inform the choice of chemotherapy for relapsed ovarian cancer are the TFI and platinum- free interval (PFI). The

conventional definition of platinum sensitivity is a PFI of greater than six months after cessation of the last platinum-based chemotherapy course and was based on the likelihood of disease response to platinum re-treatment in older studies [107,108]. However, in an era of more accurate imaging techniques and maintenance regimens, this definition is more complex with the conventional definition of platinum-sensitive disease becoming less useful clinically (Table 1) [109]. While the duration of response to platinum is important, retrospective data also suggest that seeking to extend the platinum-free interval itself may also help improve the patient's subsequent response to platinum re-treatment and there are now several studies supporting this concept [110,111]. In patients with platinum-sensitive or partially platinum-sensitive ovarian cancer recurrence (6–12 months PFI) published clinical evidence reports response rates to second-line therapy ranging between 27% and 33%, regardless of whether platinum-based or non-platinum drugs are used. However, response rates can be a poor measure of benefit, which is better expressed in terms of PFS and combination therapy (such as carboplatin/paclitaxel, carboplatin/liposomal doxorubicin or carboplatin/gemcitabine) would be recommended as this improves PFS and OS in this group of patients [107,112,113]. Trabectedin and pegylated liposomal doxorubicin (PLD) have been shown to be more beneficial compared with PLD alone, especially in the group of patients with partially platinum-sensitive disease. The addition of bevacizumab to relapse chemotherapy in the platinum sensitive setting and as maintenance afterwards also increases PFS compared with combination carboplatin/gemcita-bine alone [85,114]. In the platinum refractory/resistant setting there does not appear to be any advantage in using combination therapies, which are associated with higher rates of adverse events. In the platinum-resistant setting, second-line single-agent chemotherapy with non-platinum drugs (such as PLD, weekly paclitaxel, etoposide or topotecan) results in short-lived response rates of approximately 10–25% and PFS of 4–5 months and OS of 12–13 months [96]. However, the addition of bevacizumab to conventional chemo-therapy has been shown to increase PFS to 6.7 months, with OS of 16.6 months compared to monotherapy (PLD, weekly paclitaxel or topotecan) and improved patient-related Enpunkte in a carefully selected population [115]. If the patient cannot tolerate chemo-therapy and/or symptoms are not requiring a rapid response to chemotherapy, then hormonal treatment could be an alternative, although evidence for benefit is limited [116,117]. Palliative radiation may have a role in highly selected situations.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2019) am 02.05.2019

#	Search
1	[mh "ovarian neoplasms"] OR [mh "fallopian tube neoplasms"] OR [mh "peritoneal neoplasms"]
2	(ovar* OR ("fallopian tube" OR tubal) OR (primary AND peritone*) OR "serous surface papillary"):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions*):ti,ab,kw
4	#2 AND #3
5	{OR #1,#4}
6	#5 with Cochrane Library publication date from Jan 2014 to present

Systematic Reviews in Medline (PubMed) am 02.05.2019

#	Search
1	ovarian neoplasms/therapy[mh] OR fallopian tube neoplasms/therapy[mh] OR peritoneal neoplasms/therapy[mh]
2	carcinoma, ovarian epithelial[mh]
3	ovar*[tiab] OR ("fallopian tube"[tiab] OR tubal[tiab]) OR (primary[tiab] AND peritone*[tiab]) OR "serous surface papillary"[tiab]
4	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]
5	#3 AND #4
6	(#5) AND (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])
7	#1 OR #2 OR #6
8	(#7) 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 studies[pt] OR validation studies[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]))))))
9	((#8) AND ("2014/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Guidelines in Medline (PubMed) am 02.05.2019

#	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]
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 ("2014/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp])

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