Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-137 Rucaparib (Erhaltungstherapie)

Stand: September 2018

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

Rucaparib
[zur Erhaltungstherapie des platinsensitiven Rezidivs eines Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms]

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 Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Keine*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Olaparib (Beschluss vom 27. November 2015) – Erhaltungstherapie des serösen epithelialen Ovarialkarzinom, Eileiterkarzinom oder Peritonealkarzinoms • Niraparib (Beschluss vom 7. Juni 2018) - Erhaltungstherapie des serösen epithelialen Ovarialkarzinom, Eileiterkarzinom oder Peritonealkarzinoms
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:	
Rucaparib L01XX55 Rubraca®	<u>Zugelassenes Anwendungsgebiet</u> 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).
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.
Carboplatin L01XA02 Carboplatin Kabi®	Carboplatin wird verwendet für die Behandlung von fortgeschrittenem epithelialem Ovarialkarzinom als: • Second-Line Therapie, wenn eine andere Behandlung nicht erfolgreich war.
Cisplatin L01XA01 Cisplatin Teva®	Cisplatin Teva® wird angewendet zur Behandlung des: • fortgeschrittenen oder metastasierten Ovarialkarzinoms
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: • Fortgeschrittenes Ovarialkarzinom
Doxorubicin L01DB Ribodoxo®	Fortgeschrittenes Ovarialkarzinom
Doxorubicin *(liposomal)*	Caelyx ist indiziert:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01DB01 Caelyx®	• Zur Behandlung von Patientinnen mit fortgeschrittenem Ovarialkarzinom nach Versagen einer platinhaltigen First-Line-Chemotherapie.
Epirubicin L01DB03 Epimedac®	Epirubicin wird zur Behandlung folgender neoplastischer Erkrankungen eingesetzt: • fortgeschrittenes Ovarialkarzinom
Etoposid L01CB01 Vepesid®	In der Monotherapie ist Vepesid K angezeigt • zur palliativen systemischen Behandlung fortgeschrittener Ovarialkarzinome nach Versagen von platinhaltigen Standardtherapien.
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.
Melphalan L01AA03 Alkeran®	Fortgeschrittenes Ovarialkarzinom nach Versagen der Standardtherapie.
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.
Olaparib L01XX46 Lynparza™	Lynparza wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines BRCA-mutierten (Keimbahn und/oder somatisch) high-grade serösen epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die auf eine Platin-basierte Chemotherapie ansprechen (vollständiges oder partielles Ansprechen). Lynparza wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines high-grade epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die auf eine Platin-basierte Chemotherapie ansprechen (vollständig oder partiell).
Paclitaxel L01CD01	Zur Second-line-Chemotherapie des Ovarialkarzinoms ist Paclitaxel-GRY® bei Patientinnen mit metastasierendem Ovarialkarzinom nach Versagen einer Standardtherapie mit platinhaltigen Arzneimitteln angezeigt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Paclitaxel-GRY®	
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) ist indiziert für die Behandlung von Patientinnen mit einem platinsensiblen Ovarialkarzinomrezidiv.
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: 2018-B-137 (Rucaparib, Erhaltungstherapie)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. August 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BGCS	British Gynaecological Cancer Society
DAHTA	DAHTA Datenbank
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
EGFR	Epidermal Growth Factor Receptor
EOC	Epithelial ovarian cancer
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LL	Leitlinie
LoE	Level of Evidence
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PFS	Progression free-survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Indikation B (Erhaltungstherapie)

Erhaltungstherapie zur Behandlung von Patientinnen mit rezidivierendem, epithelialem Ovarial-, Eileiter- oder Peritonealkarzinom, welche vollständig oder partiell auf platinbasierte Chemotherapie ansprechen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Ovarial-, Eileiter- und Peritonealkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, 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 1380 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. Nachträglich wurde ein Beschluss des G-BA aufgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2015 [4].

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

Olaparib (Lynparza™) wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines BRCA-mutierten (Keimbahn und/oder somatisch) high-grade serösen epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die auf eine Platin-basierte Chemotherapie ansprechen (vollständiges oder partielles Ansprechen).

Olaparib 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 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Ausmaß des Zusatznutzens

Nicht quantifizierbar

G-BA, 2018 [3].

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.

Ausmaß des Zusatznutzens

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 [14].

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:

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

Endpunkt:

- 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

Heterogenität:

- visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs involving 599 women with EOC (3 zu Olaparib)

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.

Kaye SB, Lubinski J, Matulonis U, Ang J E, Gourley C, Karlan BY, 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. Journal of Clinical Oncology 2012;30(4):372-9.
Kummar S, Fleming GF, Oza AM, Sullivan DM, Gandara DR, Naughton M, et al. Randomized trial of oral cyclophosphamide and veliparib in high-grade serous ovarian, primary peritoneal, or fallopian tube cancers, or BRCA-mutant ovarian cancer. Clinical Cancer Research 2015;14:2562. [DOI: 10.1158/1078-0432.CCR-14-2565]CENTRAL
Kummar S, Oza A, Fleming G, Sullivan D, Gandara D, Erlichman C, et al. Randomized trial of oral cyclophosphamide © with or without veliparib (V), an oral poly (ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent BRCA-positive ovarian, or primary peritoneal or high-grade serous ovarian carcinoma. 2012 ASCO Annual Meeting. Journal of Clinical Oncology 2012;30(15 Suppl):5020. [http://meetinglibrary.asco.org/content/98169-114]CENTRAL

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira Frommer R, Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, Matulonis U. Phase 2 randomized placebo-controlled study of olaparib (AZD2281) in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). International journal of gynecological cancer. 2011; Vol. 21 (S13). CENTRAL
Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott CL, Meier W, Shapira-Frommer R, Safra T, Matei D, Fielding A, Spencer S, Dougherty B, Orr M, Hodgson D, Barrett JC, Matulonis U. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet oncology 2014;15(8):852-861
Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. New England Journal of Medicine 2012;366(15):1382-92.

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott CL, Meier W, Shapira-Frommer R, Safra T, Matei D, Fielding A, Spencer S, Dougherty B, Orr M, Hodgson D, Barrett JC, Matulonis U. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Obstetrical & gynecological survey 2015;69((10)):594-596. CENTRAL
Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote IB, Rustin GJS, Scott C, Meier W, Shapira-Frommer R, Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, Matulonis U. Phase II randomized placebo-controlled study of olaparib (AZD2281) in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). Journal of clinical oncology. 2011; Vol. 29. CENTRAL
Matulonis UA, Harter P, Gourley C, Friedlander M, Vergote IB, Rustin GJS, Fielding A, Spencer S, Ho TW, Ledermann JA. Analysis of intermediate clinical endpoints from a Phase II trial of olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). Gynecologic oncology 2014;Conference: 45th Annual Meeting on Women's Cancer of the Society of Gynecologic Oncology, SGO 2014 Tampa, FL United States. Conference Start: 20140322 Conference End: 20140325. Conference Publication:(var.pagings):54-55. 2014. CENTRAL

Oza A, Cibula D, Oaknin Benzaquen A, Poole C, Mathijssen RHJ, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase II trial. Lancet Oncology2015;; Vol. 16, issue 1:87-97. CENTRAL
Oza AM, Cibula D, Oaknin A, Poole CJ, Mathijssen RHJ, Sonke GS, et al. Olaparib plus paclitaxel plus carboplatin (P/C) followed by olaparib maintenance treatment in patients (pts) with platinum-sensitive recurrent serous ovarian cancer (PSR SOC): A randomized, open-label phase II study. Journal of Clinical Oncology 2012;30(15 Suppl):5001. [http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/5001]
Oza AM, Cibula D, Oaknin Benzaquen A, Poole CJ, Mathijssen RHJ, et al. Olaparib plus chemotherapy, followed by maintenance monotherapy, in women with platinum-sensitive recurrent serous ovarian cancer (PSR SOC): BRCA1/2 mutation (BRCAm) and interim overall survival analyses. European Journal of Cancer 2013;49 Suppl 2:S712-S3.

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.

Kommentare zum Review

- In Kaye 2012 auch platinresistente Frauen eingeschlossen
- Eine weitere Studien zu Veliparib hier nicht dargestellt wegen fehlender Zulassung

3.3 Systematische Reviews

Studien zu Bevacizumab

Ruan G et al., 2018 [11].

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

Endpunkt:

- 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

Heterogenitätsmaß:

I^2 (I^2 <50%: fixed effect model)

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 studies (n=4994)

Charakteristika der Population:

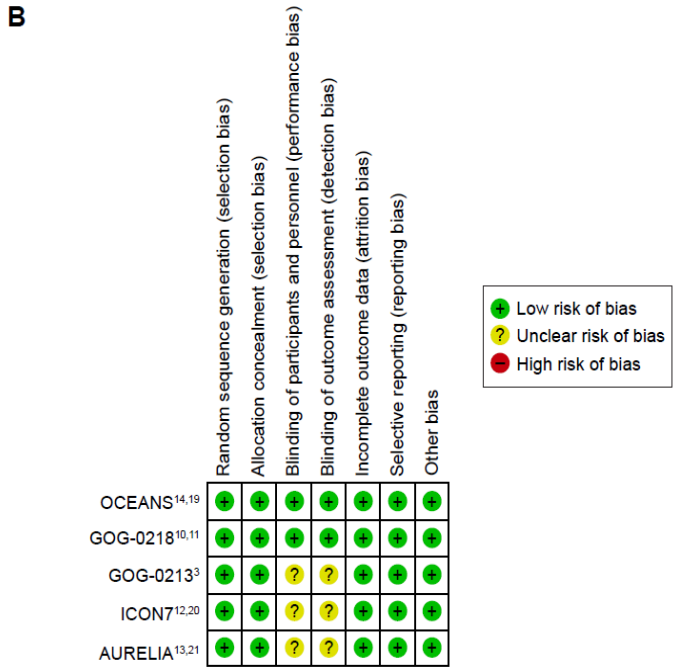
Table 1 Characteristics of included studies

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:

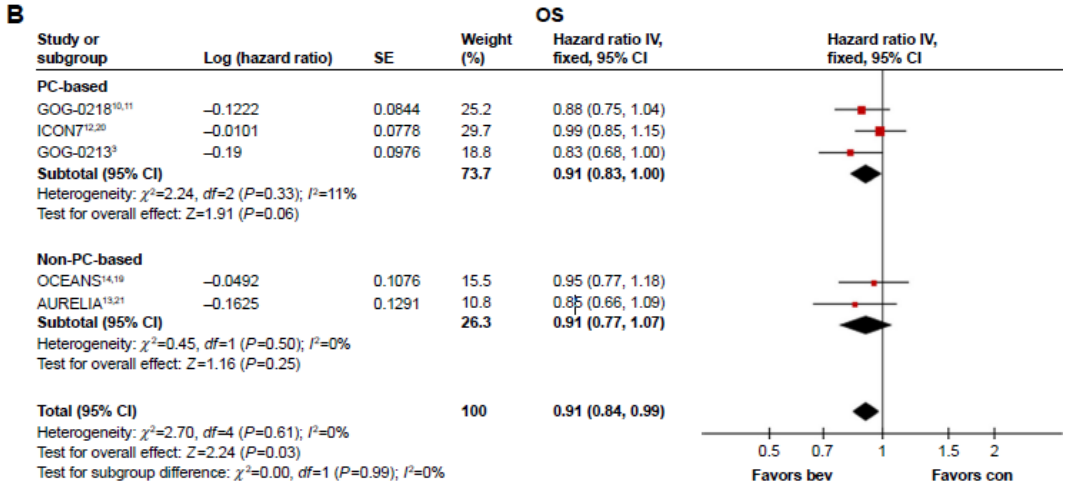
Five published studies3,11–14 showed a low risk of bias in randomized sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases; meanwhile, blinding exhibited a low risk of bias in two published studies11,14 and was unclear in three open-label published studies.3,12,13



Studienergebnisse:

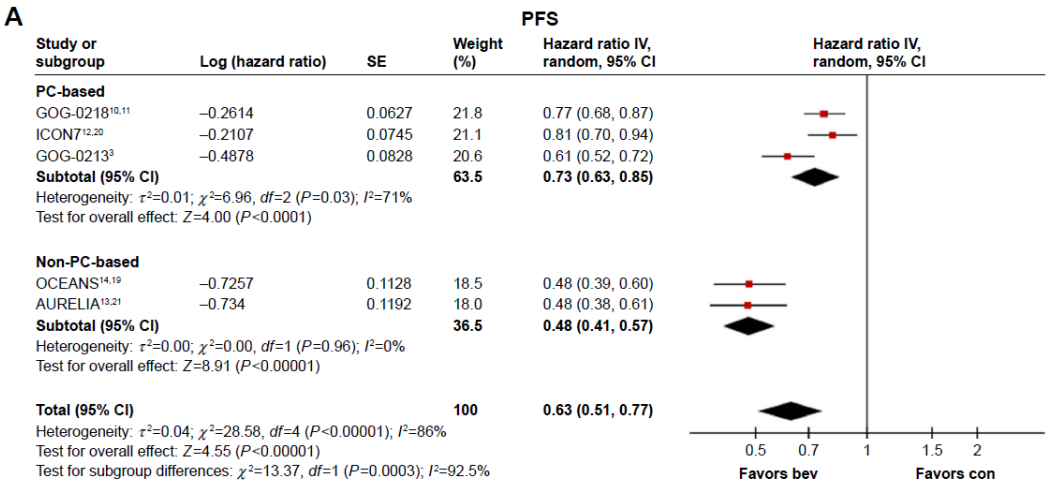
OS

- PC-based: The other trial, GOG-0213, in which the primary endpoint was OS, showed results that were close to statistical significance for OS (adjusted HR =0.829; 95% CI, 0.683–1.005; P=0.056).
- Non-PC based: OCEANS: HR [95% CI]: 0,95 [0,77; 1,18]



PFS

- PC-Based: GOG-0213: HR [95% CI]: 0,61 [0,52; 0,72]
- Non-PC-Based: OCEANS: HR [95% CI]: 0,48 [0,39; 0,60]



Referenzen (recurrent setting)

3. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18:779–791.

14. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012;30:2039–2045.

19. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. 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;139:10–16.

13. 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. J Clin Oncol. 2014;32:1302–1308.

21. Poveda AM, Selle F, Hilpert F, et al. Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA trial. J Clin Oncol. 2015;33:3836–3838.

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.

Kommentare zum Review

- Darstellung aktueller Daten zu den Studien GOG-0213 und OCEANS

Wang H et al., 2018 [13].

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

Fragestellung

We did a systematic review and meta-analysis of RCTs comparing angiogenesis inhibitors containing therapy with conventional chemotherapy alone or no further treatment for ovarian cancer to reassess the efficacy and safety of angiogenesis inhibitors in different clinical setting, including newly diagnosed ovarian cancer, recurrent patients, and pure maintenance setting.

Methodik

Population:

- women with histologically proven epithelial ovarian cancer of any stage (age, Q18 years),

Intervention und Komparator:

- angiogenesis inhibitors plus conventional chemotherapy to conventional chemotherapy alone
- angiogenesis inhibitors to no further treatment

Endpunkt:

- OS, PFS, and incidence of adverse events

Recherche/Suchzeitraum:

- We searched PubMed, EMBASE, Central (Cochrane clinical trials database) database, and clinicaltrial.gov. We searched the database from 1994 to March 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Heterogenität:

- I2 (I2 9 50%indicated a moderate to-high heterogeneity), Cochrane Q-test.
- PFS, toxicity: random effect model; OS: fixed effect model

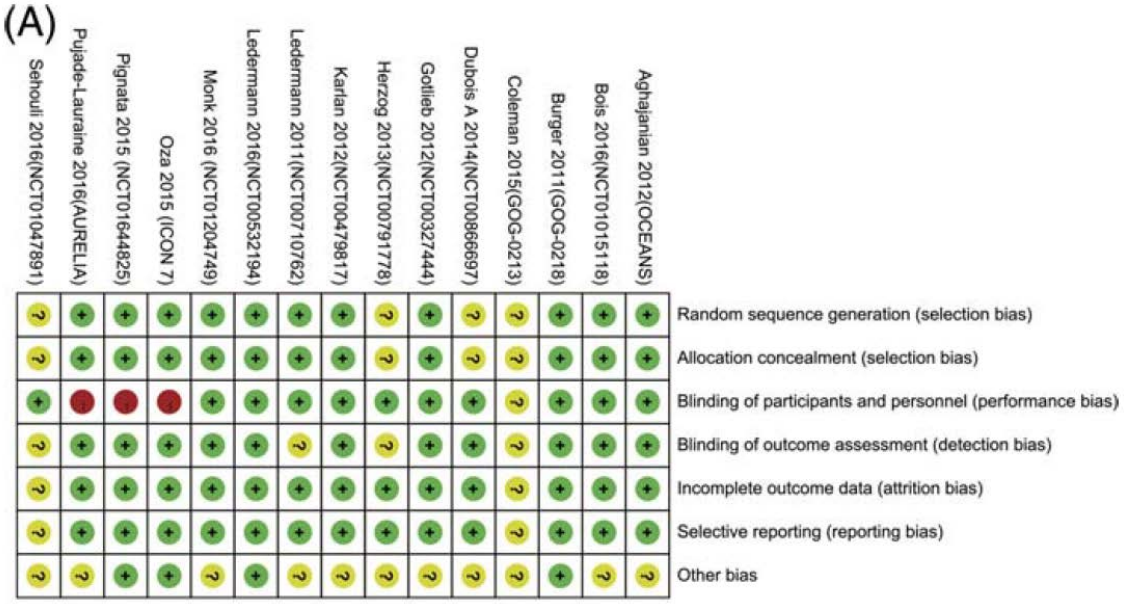
Ergebnisse

Anzahl eingeschlossener Studien:

- 15 trials (with data for 8721 participants)

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,28,29 for which ‘‘Randomize’’ was used in abstract and text, but further details were not reported, and none was stopped early.
- Moreover, 3 studies22,23,27 lacked blinding to participants and personnel, the other 2 trials25,29 did not specify whether data collectors and outcome assessors were masked to treatment allocation, and only 43,22,27,30 were not funded by industry.



Studienergebnisse:

- Auswahl an Studien mit zugelassenen AM (Bevacizumab)

References	Arms	Size	Patients Enrolled	Primary Endpoint	PFS			OS		
					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

21. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012;30:2039Y2045.
16. Coleman RL, Brady MF, Herzog TJ, et al. A phase II randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinumsensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Gynecol Oncol. 2015;137:3Y4.
23. 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. J Clin Oncol. 2014;32:1302Y1308.

Anmerkung/Fazit der Autoren

Our findings clearly lend support to the use of angiogenesis inhibitors in combination with chemotherapy in the clinical management of patients with newly diagnosed (especially for high-risk patients) or recurrent ovarian cancer. However, no statistically significant clinical benefit was identified in the pure maintenance settings.

Kommentare zum Review

Update zum Review von Li X et al., 2016 [8], allerdings mit anderer Fragestellung. Li X et al.: Analyse in Abhängigkeit der WS-Klasse bzw. Wirkstoff. Aktueller Review: Analyse in Abhängigkeit der Therapielinie.

Li X et al., 2016 [8].

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

Zhou et al., 2013 [17]. Phase III Trials of Standard Chemotherapy with or without Bevacizumab for Ovarian Cancer: A Meta-Analysis

Li J et al., 2015 [7]. Addition of bevacizumab to chemotherapy in patients with ovarian cancer: a systematic review and meta-analysis of randomized trials

Miao H et al., 2017 [9]. 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

Endpunkt:

- progression-free survival (PFS) and overall survival (OS)

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Jadad Scale

Heterogenität:

- I^2: An I^2 value>25% was considered to be large. When there was no statistically significant heterogeneity, a pooled effect was calculated with a fixed-effects model; otherwise, a random-effects model was used.

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:

- Four trials with a VEGF inhibitor (the bevacizumab group) 4–7 (throughout treatment)

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

Qualität der Studien:

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

Studienergebnisse:

First Author /ear/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)

Toxicity

- 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%, P50.001).
- 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).

6. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45
7. 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. J Clin Oncol 2014;32:1302-8

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

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Wu Y et al., 2017 [15]:

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

Endpunkt:

- OS, PFS, adverse events

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Heterogenität:

I^2 (large heterogeneity: $I^2 \leq 75\%$; random effect model for meta-analysis)

Ergebnisse

Anzahl eingeschlossener Studien:

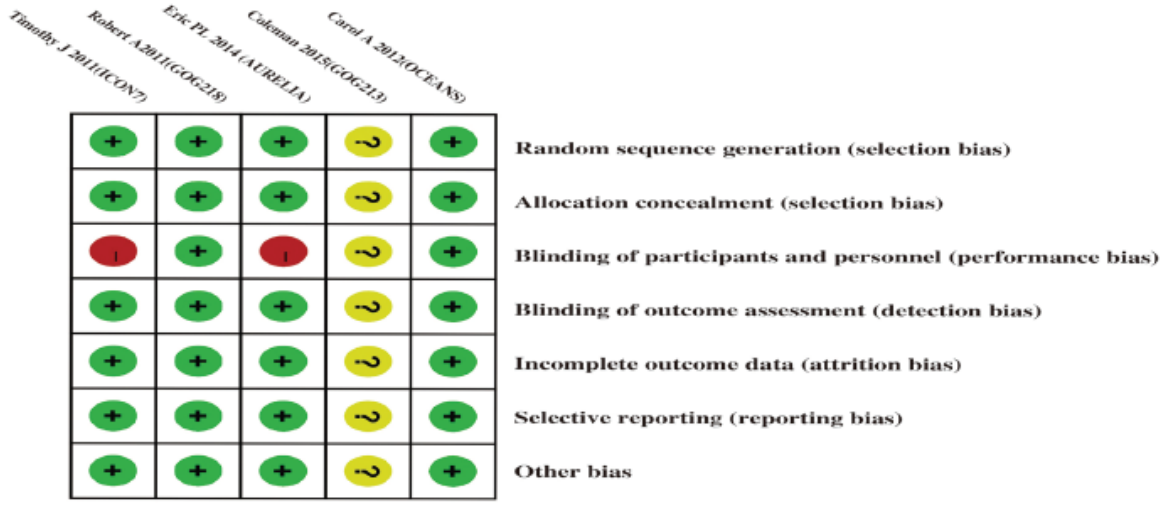
5 RCTs (n=4994)

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/m^2)+ PL, q3w Cycles 7–22: PL, q3w	Cycles 1–6: C (AUC 5 or 6)+ P (175 mg/m^2), q3w	Cycles 1–10: G (1,000 mg/m^2 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/m^2 days 1, 8, 15, and 22 q4w); or TOP (4 mg/m^2, days 1, 8, 15 q4w or 1.25 mg/m^2, days 1–5 q3w); or PLD (40 mg/m2 day 1 q4w)	Paclitaxel (175 mg/ m^2) + Carboplatin (AUC5)
Experimental arm	Cycles 1–6: C (AUC 6) + P (175 mg/m^2) + Bev (15 mg/kg), q3w Cycles 7–22: Bev (15 mg/kg), q3w	Cycles 1–6: C (AUC 5 or 6)+ P (175 mg/m^2)+ Bev (15 mg/kg), q3w Cycles 7–18: Bev (15 mg/kg), q3w	Cycles 1–10: G (1,000 mg/m^2 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/ m^2) + C (AUC5), followed by Bev maintenance

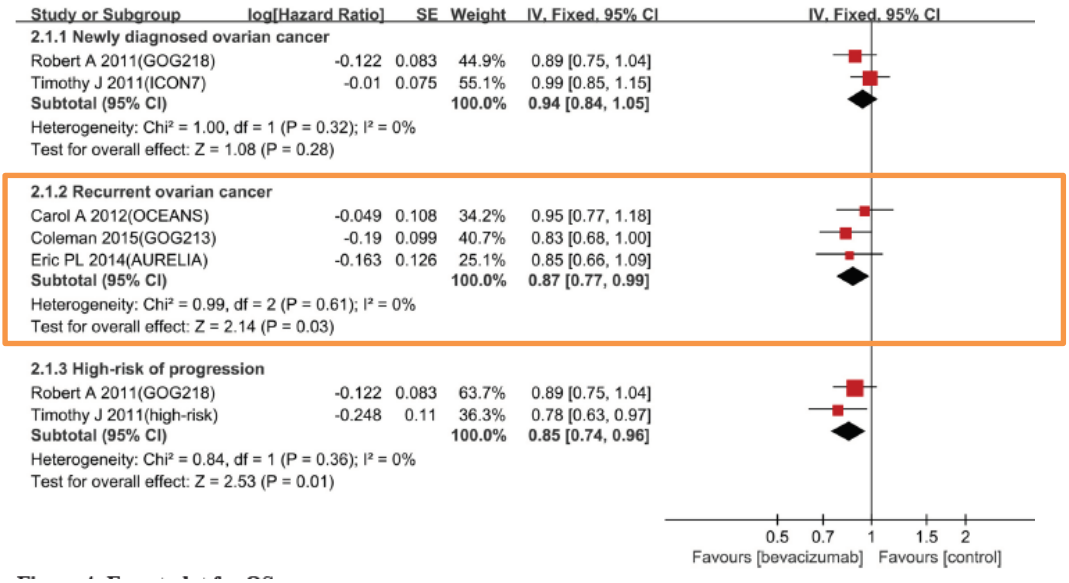
Qualitätsbeurteilung der Studien



Studienergebnisse

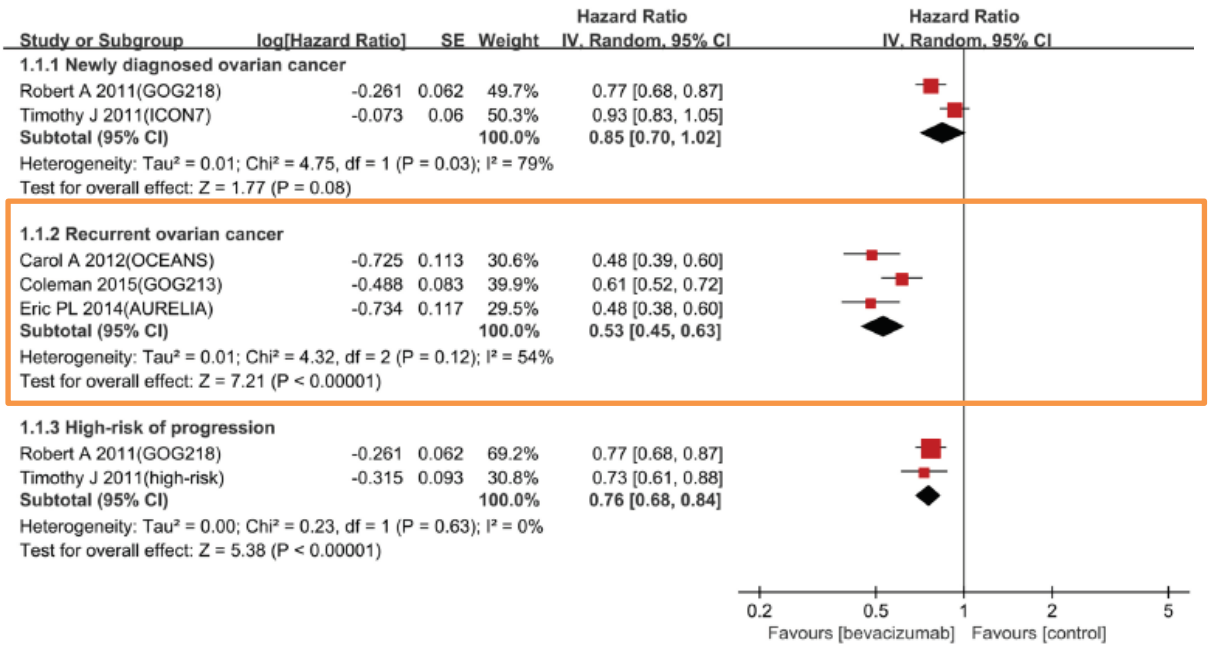
OS

- 3 RCTs; HR: 0,87 [0,77; 0,99]; p=0,03; I²: 0%



PFS

3 RCTs, HR [95% CI]: 0,53 [045; 0,63], p<0,00001; 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%)

5. R.L. Colemana MFB, M.F. Brady, T.J. Herzog, P. Sabbatini, D.K. Armstrong, J.L. Walker, B.G. Kim, K. Fujiwara, K.S.Tewari, D.M. O'Malley. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Presented at: Society of Gynecologic Oncology 2015 Annual Meeting on Women's Cancer; March 28–31, 2015; Chicago, Illinois. Abstract 3. doi:10.1016/j.ygyno.2015.01.005.

6. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. Journal of Clinical Oncology. 2014; 32: 1302-8. doi: 10.1200/JCO.2013.51.4489.

7. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR. 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. 2012; 30: 2039-45. doi: 10.1200/ JCO.2012.42.0505.

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.

Kommentar zum Review:

- Poolen von Studien zu platin-sensitivem (2 RCT) und platin-resistenten Karzinom (1 RCT)
- Ergebnisse zur Studie von Coleman et al., 2015 in Abstrakt-Form
- Studien zu platinsensitivem Karzinom: Zweitlinien-Therapie

Yi Y et al., 2017 [16].

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 + Intervention:

- chemotherapy interventions with or without antiangiogenic drugs

Endpunkt:

- 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

Heterogenität:

I^2 (fixed effect model when $I^2 \leq 50\%$)

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs with 3 RCTs with bevacizumab

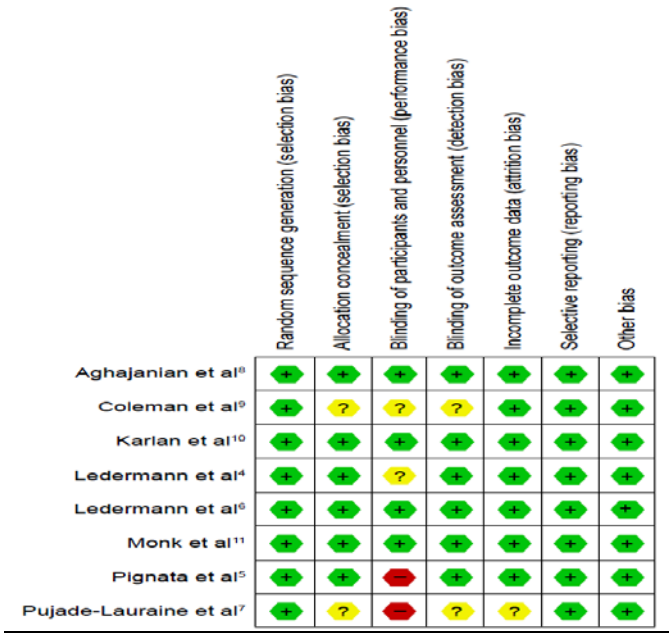
- One RCT applied antiangiogenic drugs during the maintenance phase,4 but the other drugs were fully employed from the beginning of therapy to disease progression in the other 7 RCTs.

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		
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

Qualität der Studien:



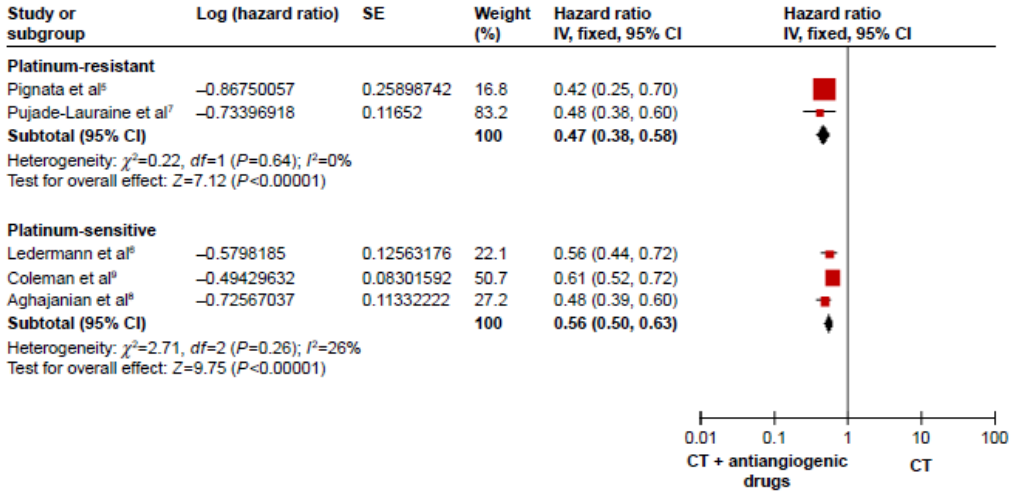
Heterogenität:

I^2 (fixed-effects model if I2≤50%)

Studienergebnisse:

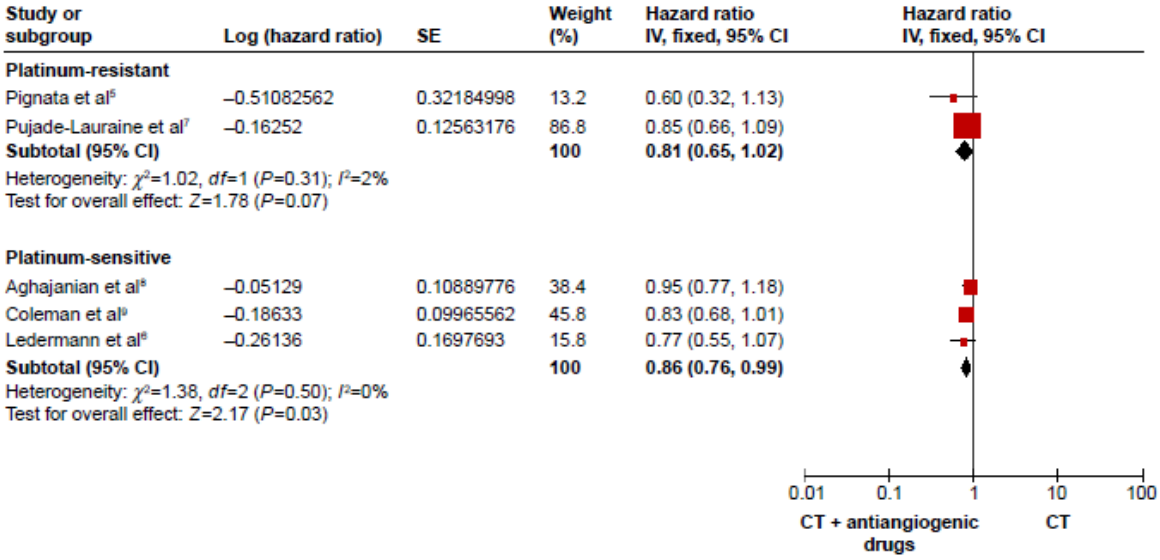
PFS

HR: 0.47, 95% CI: 0.38–0.58, I2=0%, P,0.00001



OS

HR: 0.86, 95% CI: 0.76–0.99, P=0.03



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.

Platin-sensitiv

8. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. 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):10–16.

9. Coleman RL, Brady MF, Herzog TJ, et al. Gynecologic oncology. Presented at: Society of Gynecologic Oncology 2015 Annual Meeting on Women's Cancer; March 28–31, 2015; Chicago, IL, USA. Abstract 3.
6. Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;387(10023):1066–1074.

Platin-resistent
5. Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomized, open-label, phase 2 trial. Lancet Oncol. 2015;16(5):561–568.
7. 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. J Clin Oncol. 2014; 32(13):1302–1308.

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.

Kommentar zum Review:

- Poolen von Studien mit Cediranib (nicht zugelassenes AM)
- Ergebnisse zur Zweitlinien-Therapie für Bevacizumab

Staropoli N et al., 2016 [12].

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

Endpunkt:

- 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)

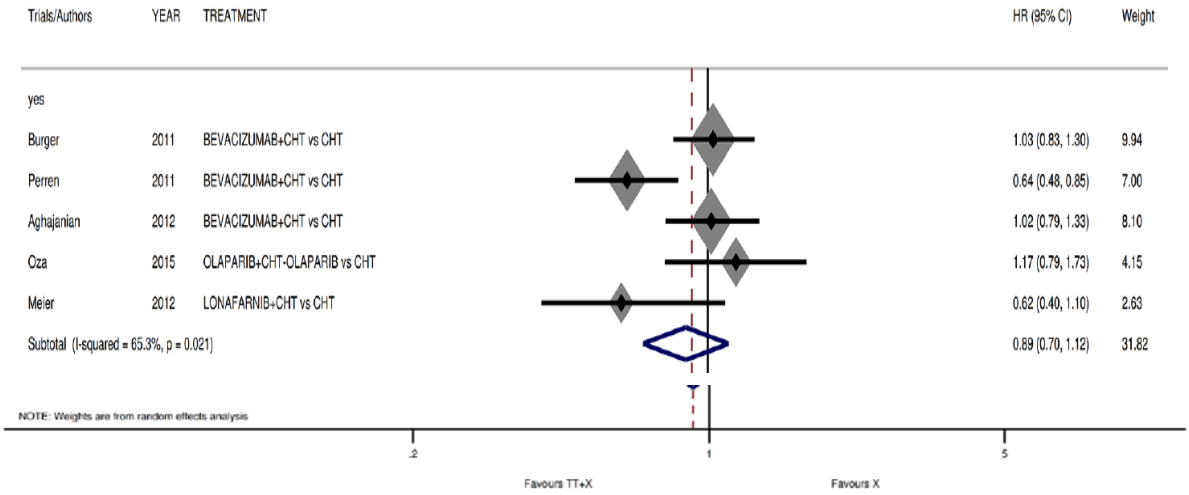
Qualität der Studien:

- 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:

Comparison of OS according to maintenance phase.

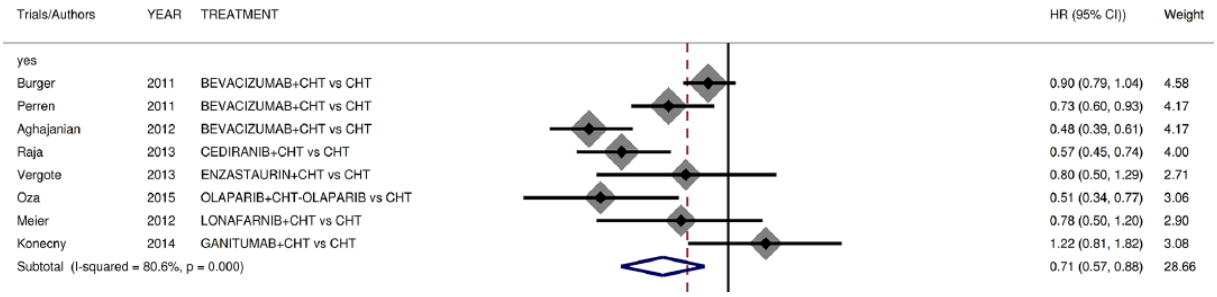
Subtotal: HR [95% CI]: 0,89 [0,70; 1,12] (I2: 65,3%)



Comparison of PFS according to maintenance phase.

- HR [95% CI]: 0,71 [0,57; 0,88] (I2: 80,6%)
- Finally, in 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.

Kommentare zum Review

- Poolen von unterschiedlichen Studien mit z.T. nicht zugelassenen AM und unterschiedlichen Therapielinien

3.4 Leitlinien

National Comprehensive Cancer Network (NCCN), 2018 [10].

Version 2.2018

Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer

Leitlinienorganisation/Fragestellung

Methodik

Grundlage der Leitlinie

Grundlage der Leitlinie

- Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen -

Recherche/Suchzeitraum:

- systematische Literatursuche

LoE und GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

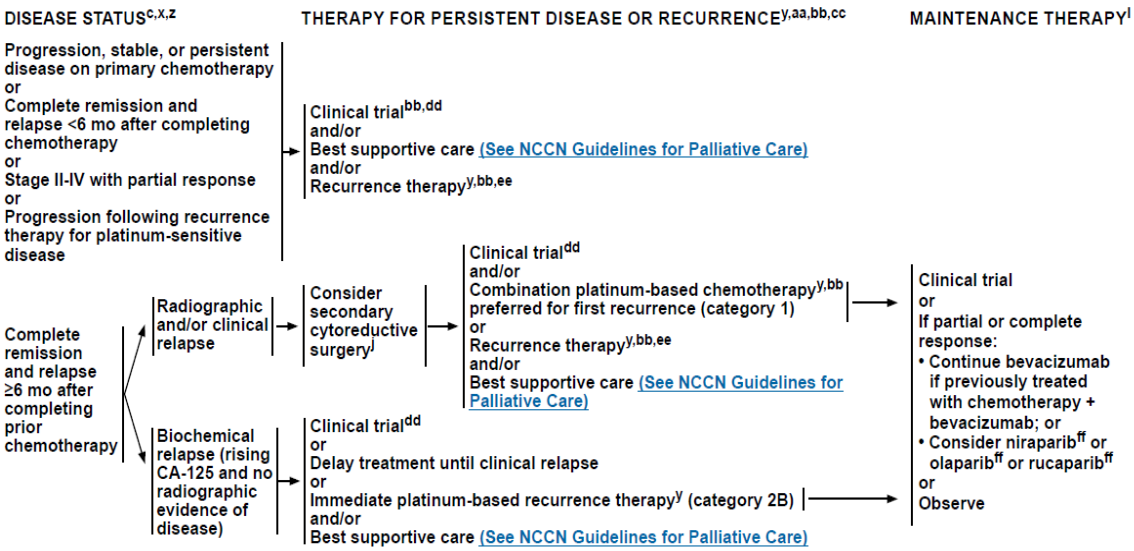
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Sonstige methodische Hinweise

- Repräsentativität der Leitliniengruppe unklar
- Systematik der Auswahl und Bewertung der Literatur unklar
- Ableitung der Empfehlungen unklar
- finanzielle Unabhängigkeit unklar
- Interessenkonflikterklärungen liegen vor

Empfehlungen



[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[i] See Principles of Surgery (OV-A).
[l] See Principles of Chemotherapy (OV-B) and Management of Drug Reactions (OV-C).
[x] Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing should include at least: *BRCA1/2*, homologous recombination pathway genes, and microsatellite instability or DNA mismatch repair.
[y] See Acceptable Recurrence Therapies (OV-B, 5 of 10).
[z] Tumor molecular testing prior to initiation of therapy for persistent/recurrent disease, if not previously done.
[aa] During and after treatment for recurrence, patients should be evaluated regularly with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.
[bb] Patients who progress on 2 consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. Decisions to offer clinical trials, supportive care only, or additional therapy should be made on a highly individual basis.
[cc] See Ancillary Palliative Surgical Procedures (OV-A 4 of 4).
[dd] Clinical trials with newer agents should be strongly considered.
[ee] There are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients with platinum-sensitive or platinum-resistant disease previously treated with bevacizumab.
[ff] For those with platinum-sensitive disease who have completed two or more lines of platinum-based therapy. Discontinue bevacizumab before initiating maintenance therapy with a PARP inhibitor.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Maintenance Therapies for Epithelial (including LCOH[j])/Fallopian Tube/Primary Peritoneal Cancer

	Regimens[a]	Recommended Use
Useful in certain circumstances	Pazopanib[y] (category 3)	Single-agent maintenance therapy if complete clinical remission following primary therapy for stage II-IV disease, if no prior bevacizumab
	Bevacizumab[n,o]	May be continued as a single-agent maintenance therapy if used previously as part of a combination therapy, if partial or complete remission following: • Primary therapy for stage II-IV disease; or • Recurrence therapy for platinum-sensitive disease
	Niraparib[x]	Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy
	Olaparib[x]	Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy
	Rucaparib[x]	Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy

Continued

[a] See Discussion for references.
[j] Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[n] There are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients with platinum-sensitive or platinum-resistant disease previously treated with bevacizumab.
[o] Contraindicated for patients at increased risk of GI perforation.
[x] Discontinue bevacizumab before initiating maintenance therapy with a PARP inhibitor.
[y] There is limited evidence that postremission pazopanib may be less effective in east Asian women with ovarian cancer. (Kim JW, Mahner S, Wu LY, et al. Pazopanib maintenance therapy in East Asian women with advanced epithelial ovarian cancer: results from AGO-OVAR16 and an East Asian study. Int J Gynecol Cancer 2018;28:2-10.)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Leitlinienprogramm Onkologie, 2017 [5,6].

DGGG, DKG, Deutsche Krebshilfe, AWMF

S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren Version 2.1 – November 2017 (erste Version von 2013)

Leitlinienorganisation/Fragestellung

Die Zielorientierung der Leitlinie umfasst die Beratung von Hochrisikogruppen, die Diagnostik, die operative und systemische Therapie der frühen und fortgeschrittenen Stadien sowie die Behandlung seltener histologischer Subtypen.

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.

- Neue Daten zur Genetik des Ovarialkarzionms
- Langzeitdaten zum Screening
- Lymphodonedektomie
- Rezidivtherapie mit PARP Inhibitoren

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

8.1.	Alte Kalendarische Einteilung der Rezidive	2013
Level of Evidence **1+**	Platinsensitives Ovarialkarzinom: Erkrankung spricht primär auf eine platinhaltige First-line-Chemotherapie an und zeigt ein Rezidiv frühestens 6 Monate nach Abschluss der platinhaltigen Chemotherapie. Darin enthalten ist die Subgruppe der partiell platinsensitiven Ovarialkarzinomrezidive. Hier spricht die Erkrankung auch primär auf eine platinhaltige First-line-Chemotherapie an, zeigt aber ein Rezidiv zwischen 6 und 12 Monate nach Abschluss der platinhaltigen Chemotherapie. Platinresistentes Ovarialkarzinom: Erkrankung zeigt ein Rezidiv innerhalb der ersten 6 Monate nach Abschluss der initialen platinhaltigen Chemotherapie. Darin enthalten ist die Subgruppe mit platinrefraktärem Ovarialkarzinomrezidiv. Hierbei spricht die Erkrankung nicht auf eine platinhaltige Chemotherapie an oder ist innerhalb von 4 Wochen nach Ende der Therapie progredient.	
	Leitlinien: SIGN [2], NHS TA91 [357] Primärstudien: [52, 422-430]	

Eine alleinige Definition der Rezidivpopulationen ausschließlich über das platin-freie Therapieintervall ist unzureichend. Die Art der Rezidivbehandlung wird von verschiedenen Faktoren bestimmt. Neben Patientinnenpräferenz, Alter und Belastbarkeit spielen auch genetische Faktoren, wie BRCA-Mutationsstatus, zurückliegende Gabe von antiangiogenetischen Substanzen oder PARP-Inhibitoren und tumorbiologische Aspekte neben dem therapiefreien Intervall eine Rolle. Die alte kalendarische Einteilung mit einem fixen cut-off von 6 Monaten und ausschließlicher Berücksichtigung des Platin-freien Intervalls ist für zukünftige Therapieentscheidungen nicht mehr ausreichend und dient vor allem noch der retrospektiven Vergleichbarkeit von Daten.

Die Rezidiv- bzw. Progressionsdiagnose kann anhand klinischer, sonographischer, histologischer, zytologischer oder radiologischer Befunde gestellt werden [429, 431]. Unter Berücksichtigung der oben aufgezählten Faktoren, muss entschieden werden, ob eine erneute platinhaltige Therapie sinnvoll erscheint (Platingeeignetes Rezidiv) oder eine nicht-platinhaltige Therapie zu bevorzugen ist (Nicht-platingeeignetes Rezidiv). Patientinnen, welche nicht im Rahmen der Primärtherapie mit Platin behandelt wurden, gelten stets als platinsensitiv.

429. Rustin, G.J., et al., Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer, 2011. 21(2): p. 419-23.
431. Eisenhauer, E.A., et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2): p. 228-47.

9.4. Vorgehen bei high grade serösem platin-sensitiven Ovarialkarzinomrezidiv mit BRCA-Mutation

8.9.	Evidenzbasierte Empfehlung	2016
Empfehlungsgrad **B**	Bei Patientinnen mit Rezidiv eines high grade serösen Ovarialkarzinoms und Nachweis einer deletären BRCA1/2 Mutation sollte eine Erhaltungstherapie mit einem PARP-Inhibitor nach Ansprechen auf eine vorherige platinhaltige Therapie angeboten werden.	
Level of Evidence **2+**	Primärstudien: [466-468]	

Patientinnen mit einem high-grade serösen Ovarialkarzinomrezidiv, die auf eine platinhaltige Chemotherapie angesprochen haben, kann eine Erhaltungstherapie mit Olaparib angeboten werden. Eine weitere Voraussetzung hierfür ist eine vorangegangene positive Testung bezüglich einer deletären BRCA1/2-Mutation.

Die Effektivität von Olaparib, einem oralen PARP-Inhibitor, als Erhaltungstherapie wurde in der Studie 19 überprüft [467]. 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 (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) [468].

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 Benefit durch eine Erhaltungstherapie (PFS median 11,2 Monate vs. 4,3 Monate; HR 0,18; 95% CI 0,11-0,31; P<0,00001).

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 %).[467].

Für das Gesamtüberleben zeigte sich kein signifikanter Unterschied [469].

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 schwache Empfehlung (Empfehlungsgrad B) abgegeben.

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 [466-468].

466. Oza, A.M., et al., Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol, 2015. 16(1): p. 87-97.
467. Ledermann, J., et al., Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol, 2014. 15(8): p. 852-61.
468. Ledermann, J., et al., Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med, 2012. 366(15): p. 1382-92.

Francis J et al., 2017 [2].

Cancer Care Ontario (CCO)

Systemic Therapy for Recurrent Epithelial Ovarian Cancer

Guideline 4-3 Version 4

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

systematische Evidenzaufbereitung (inklusive Leitlinien) - Evidenzklassifizierung und Empfehlungsgraduierung mit verschiedenen Systemen (in Evidenztabellen dargestellt) - formale Konsensusprozesse nicht regelhaft - standardisiertes Reviewverfahren (intern und extern) - Interessenkonflikterklärungen dargelegt

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from April 1, 2011 to May 30, 2017

LoE/ GoR:

GRADE strategy was used as an overall critical appraisal guide + Cochrane risk of bias tool

Empfehlungen

For patients with platinum-sensitive recurrent ovarian cancer:

- 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.

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 nonexperimental 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].

Qualifying Statements for Recommendation 4

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.

Interpretation of Evidence for Recommendation

- 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 diarrhoea due to few events in the CT arm (<5 events).

11. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, 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):2039-45.
12. Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, Rustin GJS, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;387(10023):1066-74.
13. Mirza MR, Monk BJ, Herrstedt AM, Oza A, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive recurrent ovarian cancer. N Engl J Med. 2016;375:2154-64.
14. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. 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):10-6.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 25.04.2018

#	Suchfrage
1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
2	MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees
3	MeSH descriptor: [Peritoneal Neoplasms] explode all trees
4	(ovar*):ti,ab,kw (Word variations have been searched)
5	("fallopian tube" or tubal):ti,ab,kw (Word variations have been searched)
6	((primary and peritone*) or "serous surface papillary"):ti,ab,kw (Word variations have been searched)
7	(tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or cancer*):ti,ab,kw (Word variations have been searched)
8	#4 or #5 or #6
9	#7 and #8
10	#1 or #2 or #3 or #9
11	#10 Publication Year from 2013 to 2018
12	#11 in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 25.04.2018

#	Suchfrage
1	(("ovarian neoplasms/therapy"[MeSH Terms]) OR "fallopian tube neoplasms/therapy"[MeSH Terms]) OR "peritoneal neoplasms/therapy"[MeSH Terms]
2	"ovarian epithelial cancer"[Supplementary Concept]
3	ovar*[Title/Abstract]
4	("fallopian tube"[Title/Abstract] OR tubal[Title/Abstract])
5	((primary[Title/Abstract] AND peritone*[Title/Abstract])) OR "serous surface papillary"[Title/Abstract]
6	(((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR cancer*[Title/Abstract]
7	((#3 OR #4 OR #5)) AND #6
8	(#7) AND ((((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract])) OR drug*[Title/Abstract])
9	(#1 OR #2 OR #8)
10	(#9) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND

	systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
11	((#10) AND ("2013/04/01"[PDAT] : "3000"[PDAT]))
12	(#11) NOT "The Cochrane database of systematic reviews"[Journal]
13	(#12) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
14	(#13) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 25.04.2018

#	**Suchfrage**
1	(((ovarian neoplasms[MeSH Terms]) OR fallopian tube neoplasms[MeSH Terms]) OR peritoneal neoplasms[MeSH Terms]) OR "ovarian epithelial cancer"[Supplementary Concept]
2	ovar*[Title/Abstract]
3	("fallopian tube"[Title/Abstract] OR tubal[Title/Abstract])
4	((primary[Title/Abstract] AND peritone*[Title/Abstract])) OR "serous surface papillary"[Title/Abstract]
5	(((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR cancer*[Title/Abstract]
6	((#2 OR #3 OR #4)) AND #5
7	(#1 OR #6)
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
9	(#8) AND ("2013/04/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT ((comment[ptyp]) OR letter[ptyp])
11	(#10) NOT retracted publication[ptyp]

Referenzen

1. **Ding SS, Li L, Yu CX.** Systematic evaluation of bevacizumab in recurrent ovarian cancer treatment. J BUON 2014;19(4):965-972.
2. **Francis J, Coakley N, Elit L, Kennedy EB, Mackay H, Gynecology Cancer Disease Site Group.** Systemic therapy for recurrent epithelial ovarian cancer [online]. Toronto (CAN): Cancer Care Ontario; 2017. [Zugriff: 02.08.2018]. (Program in Evidence-based Care Guideline; Band 4-3 Version 4). URL: https://www.cancercareontario.ca/en/file/34796/download?token=VMMo6sf3.
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