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 (Behandlung)

Stand: September 2018

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

Rucaparib
[zur Behandlung 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	*Keine*
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 zur Behandlung von erwachsenen Patientinnen mit platinsensitivem, rezidiviertem oder progressivem, high-grade epithelialem Ovarial-, Eileiter- oder Peritonealkarzinom mit BRCA -Mutationen (Keimbahn und/oder somatisch),die mit zwei oder mehr vorherigen platinbasierten Chemotherapielinien behandelt wurden und keine weitere platinhaltige Chemotherapie tolerieren.
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)* L01DB01 Caelyx®	Caelyx ist indiziert: • 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.
Melphalan	Fortgeschrittenes Ovarialkarzinom nach Versagen der Standardtherapie.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01AA03 Alkeran®	
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, Behandlung)

Auftrag von:	Abt. AM
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Datum:	22. August 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BGCS	British Gynaecological Cancer Society
C-P	Carboplatin - Paclitaxel
C-PLD	Carboplatin – Pegylated Liposamal Doxorubicin
DAHTA	DAHTA Datenbank
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
EGFR	Epidermal Growth Factor Receptor
EOC	Epithelial ovarian cancer
FIGO	International Federation of Gynecology and Obstetrics
G-BA	Gemeinsamer Bundesausschuss
GEM	Gemcitabin
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
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
PLD	Pegylated liposomal doxorubicin
PFS	Progression-free survival
ROC	Recurrent ovarian cancer
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TBD	Trabectedin

TOP	Topotecan
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Indikation A (Behandlung)

Zur Behandlung von erwachsenen Patientinnen mit platinsensitivem, rezidiviertem oder progressivem, high-grade epithelialem Ovarial-, Eileiter- oder Peritonealkarzinom mit BRCA-Mutationen (Keimbahn und/oder somatisch), die mit zwei oder mehr vorherigen platinbasierten Chemotherapielinien behandelt wurden und keine weitere platinhaltige Chemotherapie vertragen

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. Insgesamt ergab dies 19 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

Es konnten keine relevanten IQWiG Berichte/G-BA Beschlüsse identifiziert werden.

3.2 Cochrane Reviews

Lawrie TA et al., 2013 [5].

Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer

Fragestellung

To evaluate the efficacy and safety of PLD (Pegylated liposomal doxorubicin) in women with relapsed EOC (epithelial ovarian cancer).

Methodik

Population:

- Women with relapsed EOC of any stage, including patients with both platinum-sensitive and platinum-resistant disease.

Intervention:

- PLD in combination with platinum-based therapy versus platinum-based therapy with another agent, e.g. PLD plus carboplatin versus paclitaxel (PAC) plus carboplatin.
- Other chemotherapy agent(s) versus PLD, e.g. topotecan (TOP) versus PLD.
- PLD plus other agent(s) versus PLD alone or with placebo, e.g. trabectedin (TBD) plus PLD versus PLD.

Endpunkt:

- PFS, OS, severe adverse events, Quality of life (QoL), symptom control

Recherche/Suchzeitraum:

- 1990 until February 2013

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Heterogenität:

- T^2, I^2 and Chi^2 statistics; regarded heterogeneity as substantial if the I^2 was greater than 50% and either the T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test.

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies

Charakteristika der Population:

- PLD plus carboplatin versus platinum therapy plus another agent or alone
    - SWOG S0200 2008; HeCOG 2010; CALYPSO 2010.
    - women in whom relapse occurred more than six months after completion of a course of platinum-based chemotherapy
- Studies of other drug(s) versus PLD

- ASSIST-3 2007; Colombo 2012;Gordon 2001;Kaye 2012;MITO-3 2008;Mutch 2007; O'Byrne 2002
- Three studies included women with platinum-resistant relapsed EOC only (relapse within six months; ASSIST-3 2007; Colombo 2012; Mutch 2007); two studies included women with platinum-resistant relapsed EOC and partially platinum-sensitive relapsed EOC (relapse within 12months; Kaye 2012;MITO-3 2008); and two studies included all women with relapsed EOC(Gordon 2001; O'Byrne 2002).

- C. Studies of PLD plus other drug/s versus PLD alone
  - (ASSIST-5 2010; PRECEDENT 2013;M200 2009; OVA-301 2010).
  - Two studies included women with platinum-resistant relapsed EOC only (ASSIST-5 2010; PRECEDENT 2013) and two studies included all women with relapsed EOC (M200 2009; OVA-301 2010).
  - In these studies, one of the following agents was combined with PLD in the experimental arm and evaluated in comparison to PLD, which served as the active control
  - trabectedin (TBD): OVA-301 2010 (672 women);
  - Women in the OVA-301 2010 study had received only one prior platinum-based chemotherapy regimen, whereas the other studies included women who had received up to two previous platinum-based regimens.

Qualität der Studien:

- Allocation: Most studies weremulticentre studies with central randomisation and treatment allocation after registrationwith the organising centre, andwere therefore at a lowrisk of selection bias.
- Blinding: All of the included studies were open-label, i.e. the participants and attending healthcare professionals were aware of the associated group allocation; therefore, all studies were at a high risk of performance bias. Only six studies reported assessor blinding or independent radiologist or oncologist review.
- Incomplete outcome data: Attrition rates were high in ASSIST-3 2007 for primary outcomes and we were unable to use these data. Three other studies did not clearly state the total numbers of participants evaluated per outcome (i.e. denominators were missing).
- Most included studies reported their pre-specified outcomes. Three studies reported only limited data in the abstracts of conference proceedings that could not be adequately evaluated for reporting bias. 3 canfosfamide studies were judged to be at a high risk of reporting bias.

Studienergebnisse:

PLD plus carboplatin versus carboplatin ± other drug/s (platinsensitives Rezidiv)

Overall survival

- There was no significant difference in OS between treatment arms for the PLD/carbo versus carbo alone comparison (one study, 61 participants; HR 0.69, 95% CI 0.40 to 1.21)

(SWOG S0200 2008) or for the PLD/carbo versus PAC/carbo meta-analysis (two studies, 1164 participants; HR 1.01, 95% CI 0.88 to 1.17; I^2 = 0%; P value 0.85) (CALYPSO 2010, HeCOG 2010) (Quality of the evidence (GRADE): moderate).

Safety and adverse events

- ***PLD/carbo versus carbo alone***: Women in the combination arm were statistically significantly more likely than those in the carbo alone arm to experience neutropenia and thrombocytopenia (reduced numbers of platelets) in the one small study that evaluated this comparison (SWOG S0200 2008).
- ***PLD/carbo versusPAC/carbo***:
- Women in the PAC/carbo group were statistically significantly more likely to discontinue treatment due to toxicity than women in the PLD/carbo group (two studies, 1150 participants; RR 0.38, 95% CI 0.26 to 0.57; I^2 = 0%; P < 0.00001) (Quality of the evidence (GRADE): high).

Quality of life

- Only one study (CALYPSO2010) reported QoL outcomes. The mean change in global health scores from baseline scores was significantly better at three months post-randomisation in the PLD/carbo group versus the PAC/carbo group (P value 0.01), but not at six months.
- Scores for peripheral neuropathy (P < 0.001), other chemotherapy side-effects (P < 0.001) and body image (P value 0.02) were significantly worse in the PAC/carbo group at six months.
- These QoL data suffered from high attrition rates (greater than 30%).

Other drug(s) versus PLD

Overall survival

- Five out of seven studies contributed data to the analyses. These studies were clinically heterogeneous in terms of the comparative intervention (e.g. Gemcitabin (GEM), topotecan (TOP), Olaparib (OLA), Patupilone (PAT)) and the platinum-free interval, therefore in all analyses, we subgrouped studies by the comparative intervention and evaluated subtotals only.
- There was no statistically significant difference in OS between the GEM and PLD arms (two studies, 348 participants; HR 1.23, 95% CI 0.81 to 1.88; I^2 = 73%; P value 0.33), although the point estimate favoured the PLD arm.
  1 Studie (MITO-3 2008, N=76) bei Patientinnen mit **platin-resistentem und –teil-sensitivem Rezidiv** zeigte einen signifikanten Effekt zugunsten von PLD (HR 1.51, 95% CI 1.15, 1.98).
- 1 Studie (Mutch 2007, N=99) bei Patientinnen mit **platin-resistentem Rezidiv** zeigte einen nicht signifikanten Effekt zugunsten von GEM (HR 0.98, 95% CI 0.70, 1.38).
- None of the individual studies in any of the other subgroups (Olaparib vs. PLD, Patupilone vs. PLD) showed a statistically significant difference in OS between the experimental and PLD arms, except for the study of TOP versus PLD (Gordon 2001), where OS was significantly longer in the PLD arm (481 women; HR 1.23, 95% CI 1.01 to 1.50). **(platinresistent and –sensitive)**

Safety and adverse events

The statistically significant differences between interventions with regard to G3 to 4 severe adverse events were as follows (by subgroup):

GEM versus PLD (two studies; 338 women):

- hand-foot syndrome, RR 0.07 (95% CI 0.01 to 0.54) in favour of GEM;
- neutropenia, RR 2.25 (95% CI 1.46 to 3.47) in favour of PLD

TOP versus PLD (one study; 474 women):

- hand-foot syndrome, RR 0.01 (95% CI 0.00 to 0.15) in favour of TOP
- stomatitis, RR 0.05 (95% CI 0.01 to 0.38) in favour of TOP
- anaemia, RR 5.16 (95% CI 2.93 to 9.10) in favour of PLD
- neutropenia, RR 6.31 (95% CI 4.46 to 8.94) in favour of PLD
- thrombocytopenia, RR 27.12 (95% CI 8.69 to 84.67) in favour of PLD
- alopecia, RR 4.75 (95% CI 1.38 to 16.30) in favour of PLD

PLD plus other drug/s versus PLD alone (platinresistent and -sensitive)

- TBD (trabectedin)/PLD versus PLD (one study, 672 participants): OS was not significantly different between the treatment arms. However, the point estimate favoured the combination treatment (HR 0.86, 95% CI 0.72 to 1.02; P value 0.09) (Quality of the evidence (GRADE): moderate).
- Only the PPS (partially platinum-sensitive) ROC subgroup of arm 1 had a statistically significantly longer OS than the arm 2 subgroup (PLD alone) (HR 0.59; 95% CI 0.42 to 0.82; P value 0.0015)
- Women in the combination arm were significantly more likely than those in the PLD only arm (333 versus 330 women respectively) to experience G 3 to 4 adverse events.

Anmerkung/Fazit der Autoren

In platinum-sensitive relapsed epithelial ovarian cancer, PLD/carbo is more effective than PAC/carbo and is better tolerated; PLD/carbo should therefore be considered as first-line treatment in women with platinum-sensitive relapsed EOC. PLD alone is a useful agent for platinum-resistant relapsed EOC, however it remains unclear how it compares with other single agents for this subgroup and in what order these agents should be used. There is insufficient evidence to support the use of PLD in combination with other agents in platinum-resistant relapsed EOC.

Kommentare zum Review

- In den Studien ohne platinbasierte Therapieschemen (TOP vs. PLD und GEM vs PLD) sind teilweise platinresistente und –sensitive Frauen eingeschlossen
- UEs in der Gesamtpopulation untersucht
- Patupilone nicht zugelassen

3.3 Systematische Reviews

Studien zu Bevacizumab

Ruan G et al., 2018 [12].

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:

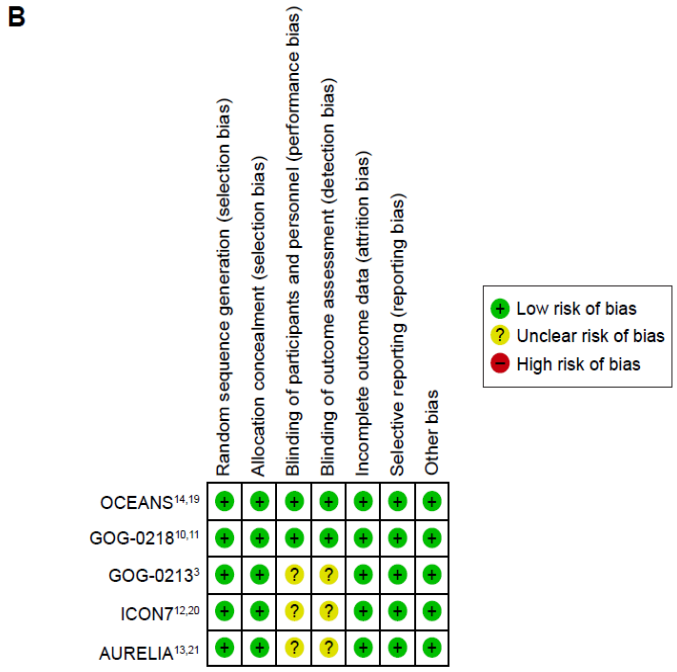
Table 1 Characteristics of included studies

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:

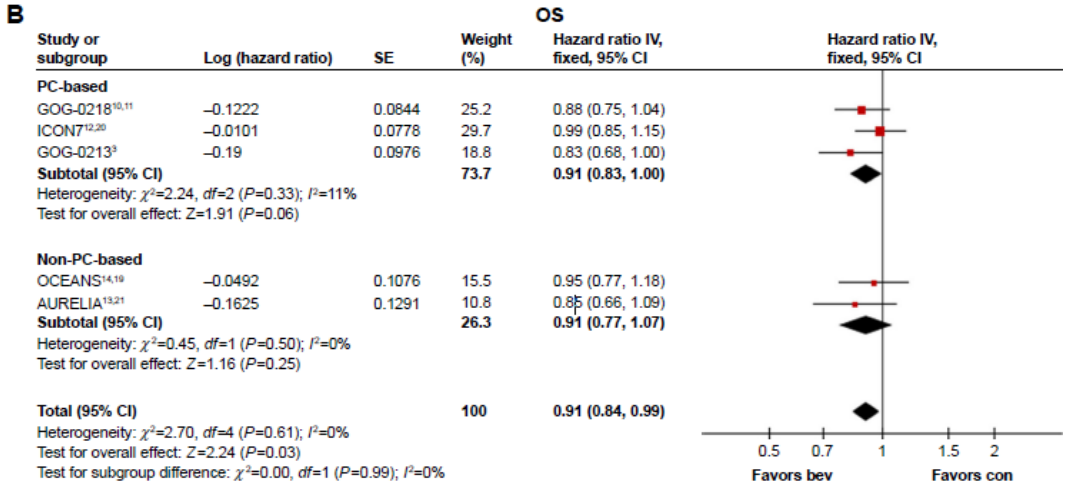
Five published studies3,11–14 showed a low risk of bias in randomized sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases; meanwhile, blinding exhibited a low risk of bias in two published studies11,14 and was unclear in three open-label published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



Studienergebnisse:

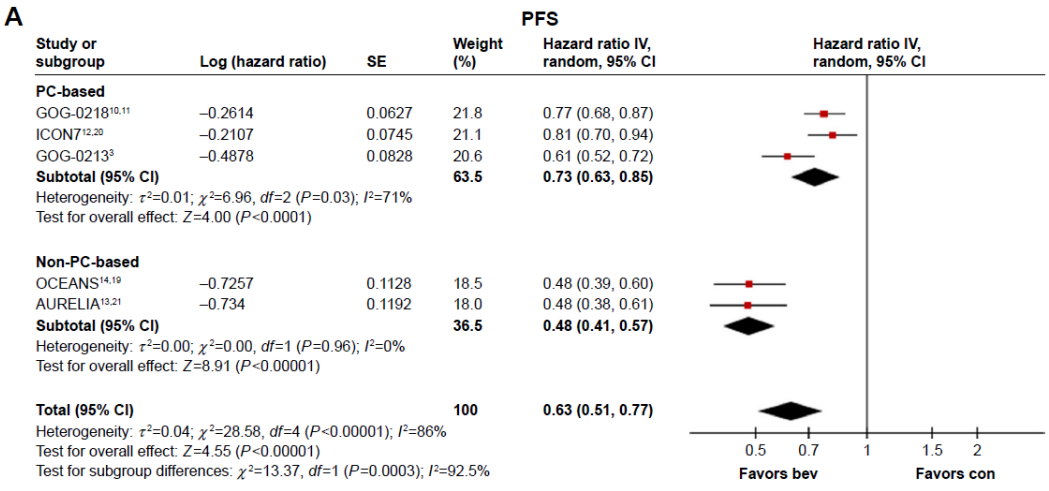
OS

- 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 [16].

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

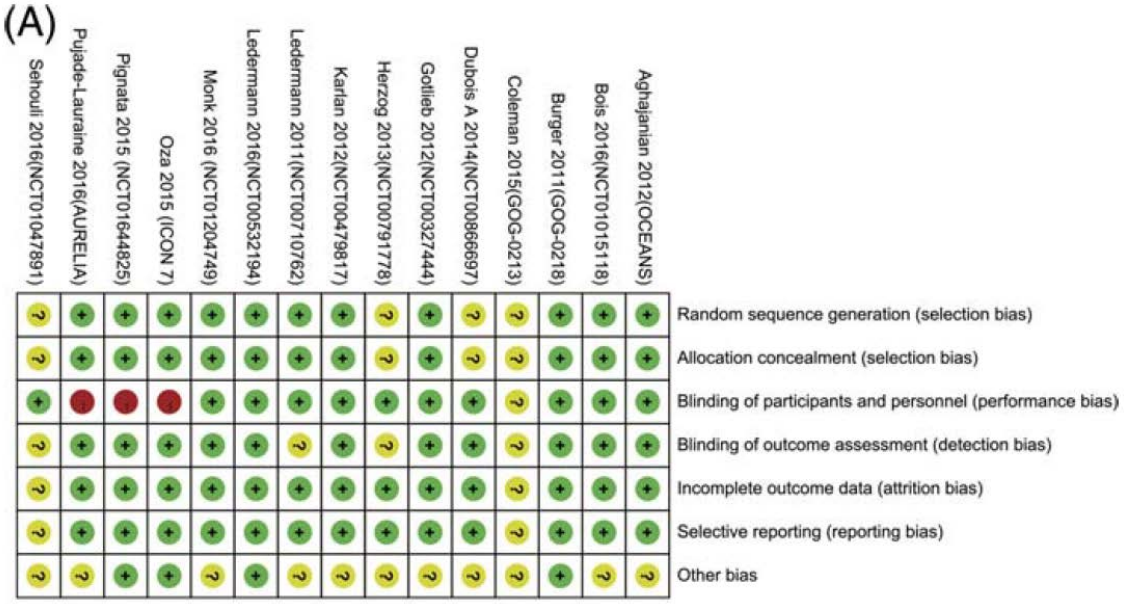
Ergebnisse

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		

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 [9], 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 [9].

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 [19]. Phase III Trials of Standard Chemotherapy with or without Bevacizumab for Ovarian Cancer: A Meta-Analysis

Li J et al., 2015 [8]. Addition of bevacizumab to chemotherapy in patients with ovarian cancer: a systematic review and meta-analysis of randomized trials

Miao H et al., 2017 [10]. 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 trials13–16 and eight phase III trials4–7,11,12,17,18 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 [17]:

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

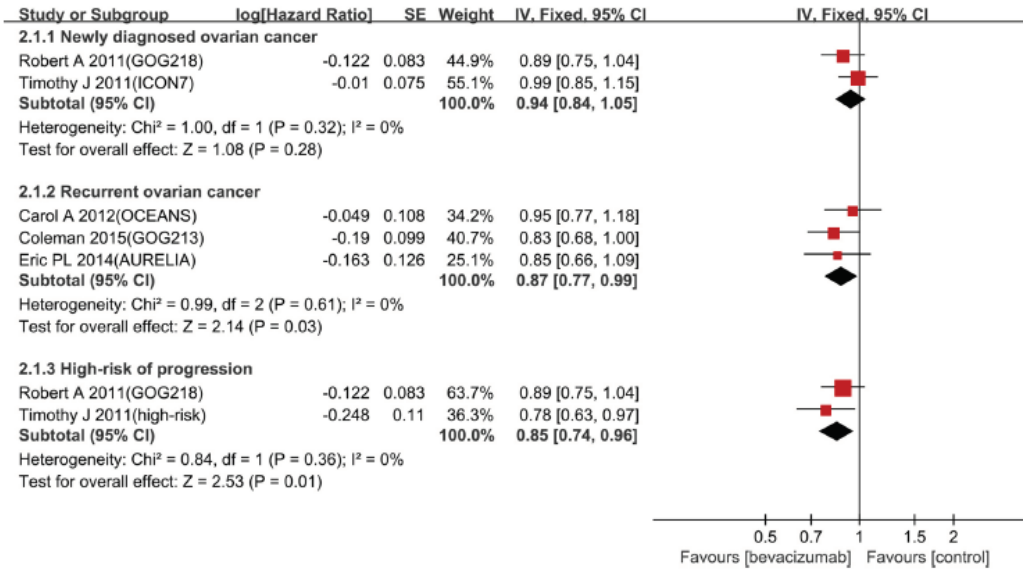
	GOG218	ICON7	OCEANS	AURELIA	GOG213
Primary endpoint	PFS	PFS	PFS	PFS	OS
Patients enrolled	Stage III (incompletely resectable) or stage IV	Stage I-III or StageIV or Inoperable Stage III	Platinum-sensitive recurrent ovarian cancer (recurrence ≥6 months after completing platinum-based therapy)	Platinum-resistant 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

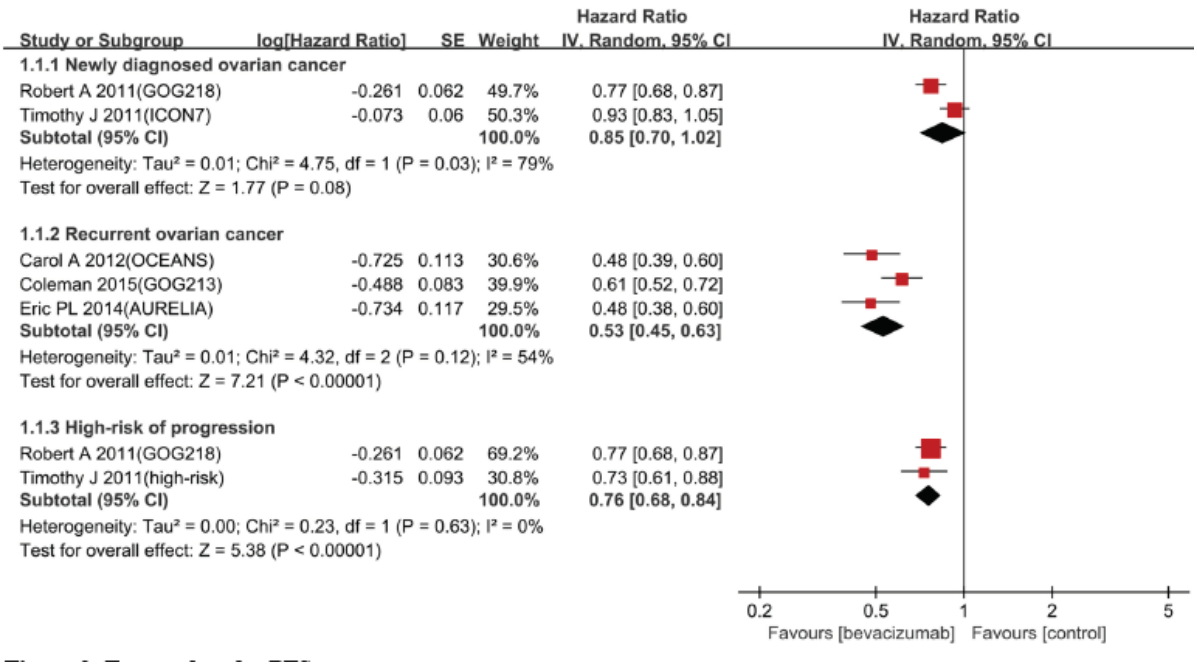
OS

- 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 [18].

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

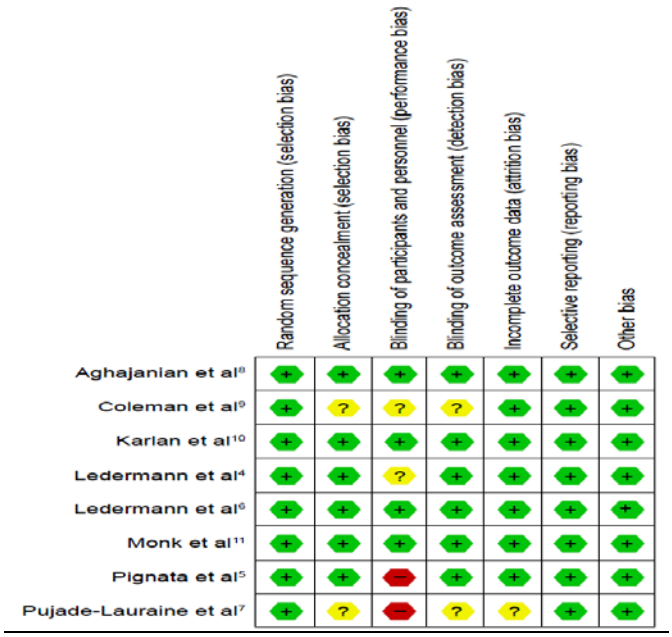
- One RCT applied antiangiogenic drugs during the maintenance phase,4 but the other drugs were fully employed from the beginning of therapy to disease progression in the other 7 RCTs.

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:

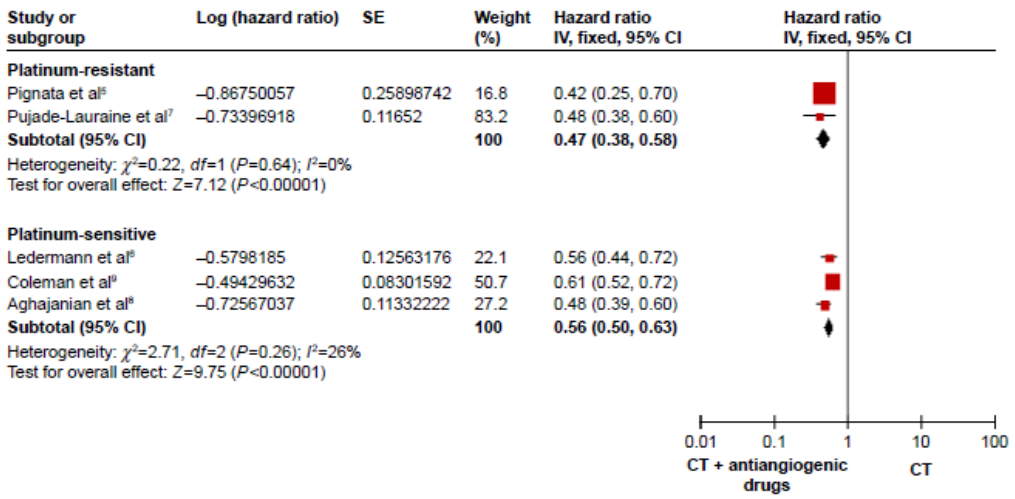


Heterogenität:

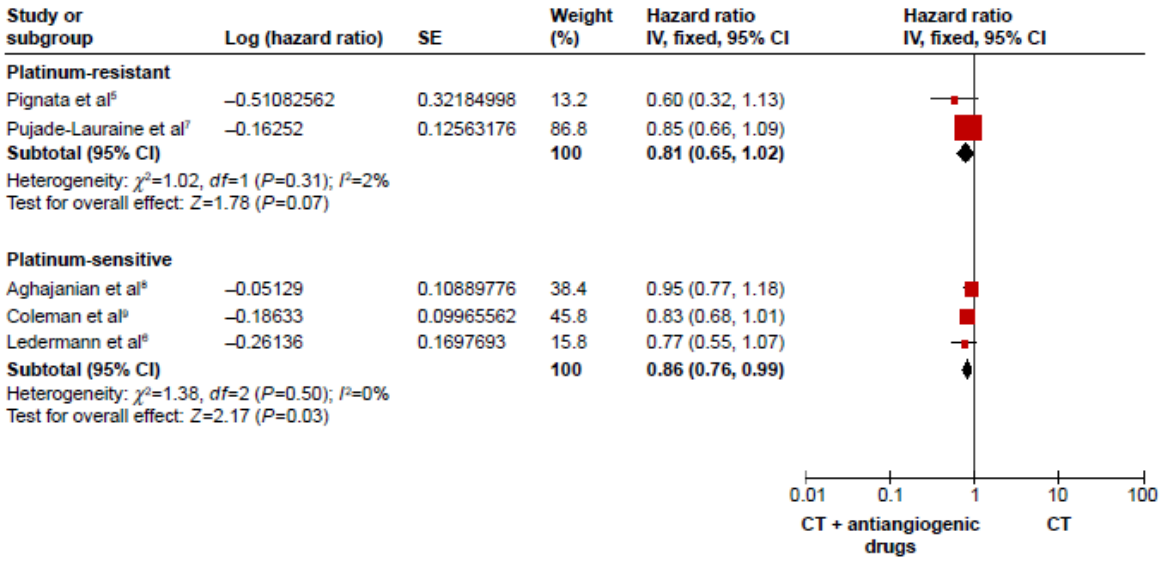
I^2 (fixed-effects model if I2≤50%)

Studienergebnisse:

PFS



OS



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 nicht zugelassenes AM
- Ergebnisse zur Zweitlinien-Therapie für Bevacizumab

Staropoli N et al., 2016 [15].

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:

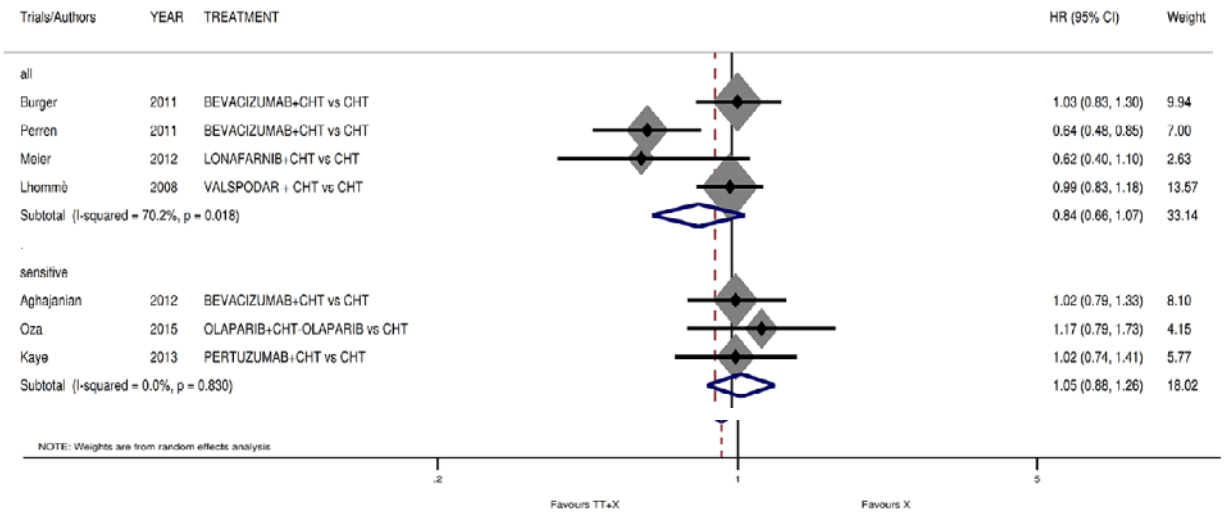
- Twenty trials were scored A (low risk of bias), 9 trials was scored B (intermediate risk of bias), and 1 trial was scored C (high risk of bias)

Studienergebnisse:

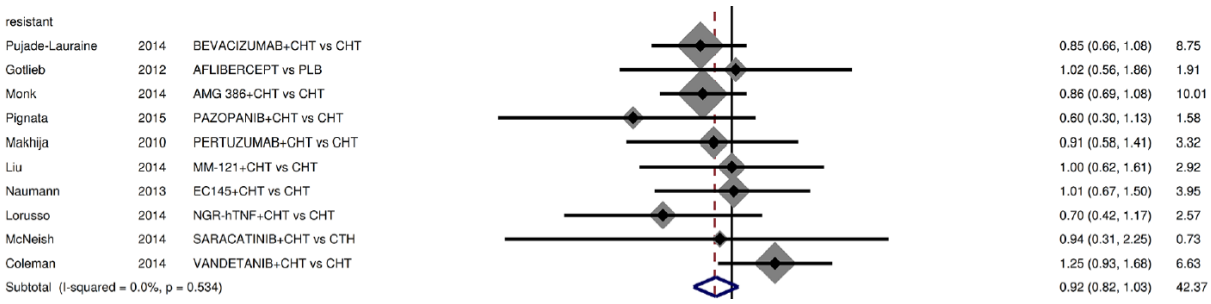
Overall survival

Comparison of OS according to platinum status.

Platinum-sensitive: Subtotal: HR [95% CI]: 1,05 [0,88; 1,26] (I2: 0,0%)



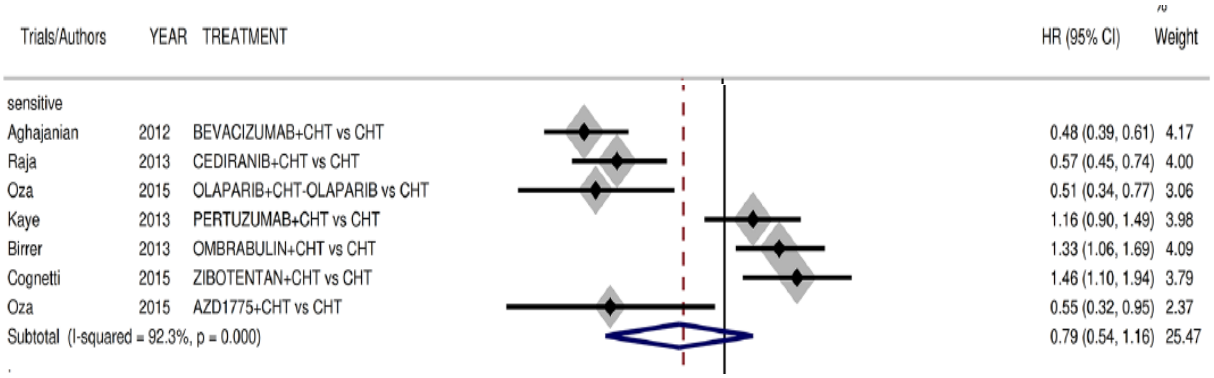
Platinum-resistant: Subtotal: HR [95% CI]: 0,92 [0,82: 1,03] (I2: 0,0%)



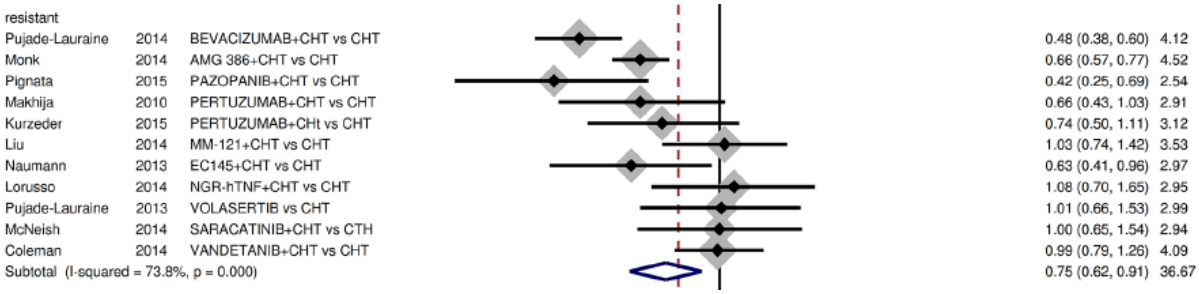
PFS

Comparison of PFS according to platinum status.

- Platinum-sensitive: Subtotal: HR [95% CI]: 0,79 [0,54; 1,16] (I2: 92,3%)



- Platinum-resistant: Subtotal: HR [95% CI]: 0,75 [0,62; 0,91] (I2: 73,8%)



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

Weitere systematische Reviews

Staropoli N et al., 2014 [14].

Pegylated liposomal doxorubicin in the management of ovarian cancer: A systematic review and metaanalysis of randomized trials

Fragestellung

Ovarian cancer is the leading cause of death among gynecological tumors. Carboplatin/paclitaxel represents the cornerstone of front-line treatment. Instead, there is no consensus for management of recurrent/progressive disease, in which pegylated liposomal doxorubicin (PLD) ± carboplatin is widely used.

Methodik

Population:

- diagnosis of OC

Intervention:

- single PLD or PLD containing regimen

Komparator:

- other single agent or PLD-free combination

Endpunkt:

- OS, PFS, response rates (RRs), CA125 response, and toxicity rates (TRs)

Recherche/Suchzeitraum:

- PubMed, Embase, the Central Registry of Controlled Trials of the Cochrane Library) and major meeting abstract databases (ASCO and ESMO) and selected studies published between January 2000, at the time of PLD treatment introduction, and January 2013

Qualitätsbewertung der Studien:

- Cochrane reviewers' handbook for 4 requirements: method of randomization, allocation concealment, blindness, and adequacy of follow-up

Heterogenität: I^2 (Fixed effect and random-effect model)

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies (n=5760)

Charakteristika der Population:

- 2 front-line (involving 1682 patients), 10 second-line (n=2788 patients, 1669 of which were platinum-sensitive and 1119 platinum-refractory), 2 third line (1290 platinum-refractory patients)

Qualität der Studien:

- Nine trials were scored A (low risk of bias), four trials were scored B (intermediate risk of bias), and one trial was scored C (high risk of bias)

Table 3. Quality assessment

Included studies	Method of randomization	Allocation concealment	Blindness	Withdrawal and dropout	Baseline	Quality level
Pignata et al.[39]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
Bookman et al.[40]	Centralized	Not detailed	No	Detailed criteria	Identical baseline	B
CALYPSO[11]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
Bafaloukos et al.[44]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
Alberts et al.[43]	Centralized	Not detailed	No	Detailed criteria	Identical baseline	B
Kaye et al.[41]	Centralized	Central office	No	Not detailed	Identical baseline	B
Ferrandina et al.[28]	Centralized	Central office	Yes	Detailed criteria	Identical baseline	A
Mutch et al.[20]	Centralized	Not detailed	No	Detailed criteria	Identical baseline	B
Gordon et al.[36]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
O'Byrne et al.[48]	Not reported	Not detailed	No	Not detailed	Identical baseline	C
AURELIA[46]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
Colombo et al.[45]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
Vergote et al.[35]	Centralized	Central office	No	Detailed criteria	Identical baseline	A
Rose et al.[47]	Centralized	Not detailed	No	Not detailed	Identical baseline	B

Studienergebnisse:

OS

- PLD was not associated with improved survival in OC patients (pooled HR: 0.94; 95% CI: 0.88–1.02; P = 0.132) and this result was confirmed in all subgroup analyses (including platinum-sensitive patients).
- The trial by Gordon et al. (sensitive + resistant) was the only RCT that reported a significant improvement in OS for PLD compared with topotecan.

PFS

- The analyses of study subgroups demonstrate a significant PFS advantage only in second-line setting (pooled HR: 0.85; 95% CI: 0.75–0.91) and in platinumsensitive patients (3 RCTs: pooled HR: 0.83; 95% CI: 0.74–0.94; I2: 62,8%)

Toxicity

- We analyzed specifically hematological toxicity: among toxicities, anemia and neutropenia were more frequent in PLD-free treatment groups; however these differences were not statistically significant.

Referenzen zu platinsensitiven Karzinom

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Anmerkung/Fazit der Autoren

According to our results, even if PLD treatment produces a minimal advantage in terms of PFS, this effect does not translate into a significant impact in terms of OS.

Gibson JM et al., 2013 [4].

The Role of Pegylated Liposomal Doxorubicin in Ovarian Cancer: A Meta-Analysis of Randomized Clinical Trials

Fragestellung

In order to elucidate the role of PLD in the treatment of ovarian cancer, we conducted this meta-analysis of randomized clinical trials to evaluate the efficacy and the toxicity of (a) a platinum-based regimen containing PLD compared with a platinum-based regimen containing a taxane and (b) PLD as a single agent compared with other single-agent regimens in the treatment of ovarian cancer.

Methodik

Population:

- histologically confirmed ovarian cancer

Intervention:

- carboplatin with PLD (C+PLD) or platinum agent

Komparator:

- carboplatin with paclitaxel (C+P) or taxane

Endpunkt:

- efficacy endpoints and adverse events

Recherche/Suchzeitraum:

- PubMed,1997–2013; ISI Web of Knowledge,2001–2013; and Scopus, 1999–2013

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Heterogenität:

- p value <.05, in accordance with the random-effects model developed by DerSimonian and Laird; fixed-effect model was used: no evidence of heterogeneity among the studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies

Charakteristika der Population (Details siehe Anhang)

- Trials included in the C+PLD versus C+P meta-analysis were all randomized multicenter studies
    - 970 patients were treated with C+PLD, and 1,015 patients were treated with C+P.
    - All patients in these three trials had platinum-sensitive ovarian carcinoma.
    - Patients in CALYPSO and Hellenic were previously treated with C+P, whereas patients in MITO-2 were chemotherapy naïve
- The trials included for the monotherapy regimens were also all phase III, randomized, multicenter trials.

- o A total of 954 patients were treated with PLD, and 1,145 patients were treated with an alternative monotherapy agent
- o All patients had histologically confirmed ovarian carcinoma, but their platinum-sensitivity status differed.

Qualität der Studien:

Trial or cohort	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Intent-to-treat analysis	Other potential threats
CALYPSO [19]	Random; permuted blocks of 6	Unclear	No	No	No	Yes	Yes
MITO-2 [9]	Random; telephone assignment	Yes	No	No	No	Yes	Yes
Hellenic [10]	Random; telephone assignment	Yes	No	Yes	Yes	No	Yes
Gemcitabine I [16]	Random; telephone assignment	Yes	Evaluators blinded	Yes	Yes	Yes	Yes
Gemcitabine II [21]	Random; unclear	Unclear	No	Yes	Yes	Yes	Yes
Topotecan I [22][a]	First step randomized; second step not randomized	Unclear	No	Yes	Yes	Yes	Yes
Topotecan II [13]	Random; unclear	Unclear	No	Yes	Yes	Yes	Yes
Canfosfamide [22][a]	First step randomized; second step not randomized	Unclear	No	Yes	Yes	Yes	Yes
Patupilone [15]	Random; telephone assignment	Yes	Evaluators blinded	Yes	Yes	Yes	Yes

[a]Canfosfamide and Topotecan I are two cohorts of the same trial comparing canfosfamide with PLD or topotecan. Patients were randomized to one of two treatment arms: canfosfamide or topotecan/PLD. Patients in the topotecan/PLD treatment arm chose one of the two treatments.

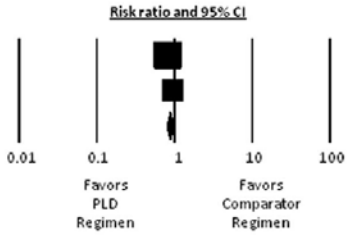
Studienergebnisse:

C+PLD versus C+P:

- OS: Meta-analysis showed no significant difference in OS between C+PLD and C+P (3 RCTs: HR, 95%CI, 0,84-1,07; p=0,36)
- PFS: Meta-analysis showed that C+PLD was associated with a significant improvement in PFS (2 RCTs: HR, 0.87; 95% CI, 0.78–0.96; p = .008)

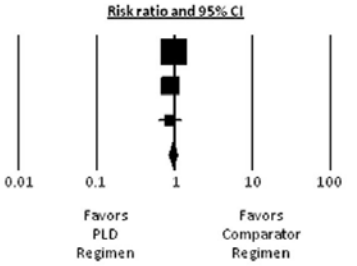
A Progression Free Survival

Study name	Risk ratio	Lower limit	Upper limit	Z value	*p* value
CALYPSO	0.820	0.718	0.937	−2.918	.004
MITO-2	0.950	0.804	1.122	−0.604	.546
Overall	0.869	0.783	0.964	−2.655	.008



B Overall Survival

Study name	Risk ratio	Lower limit	Upper limit	Z value	*p* value
CALYPSO	0.990	0.847	1.157	−0.127	.899
MITO-2	0.890	0.714	1.110	−1.034	.301
Hellenic [a]	0.876	0.618	1.242	−0.742	.458
Overall	0.946	0.840	1.066	−0.910	.363

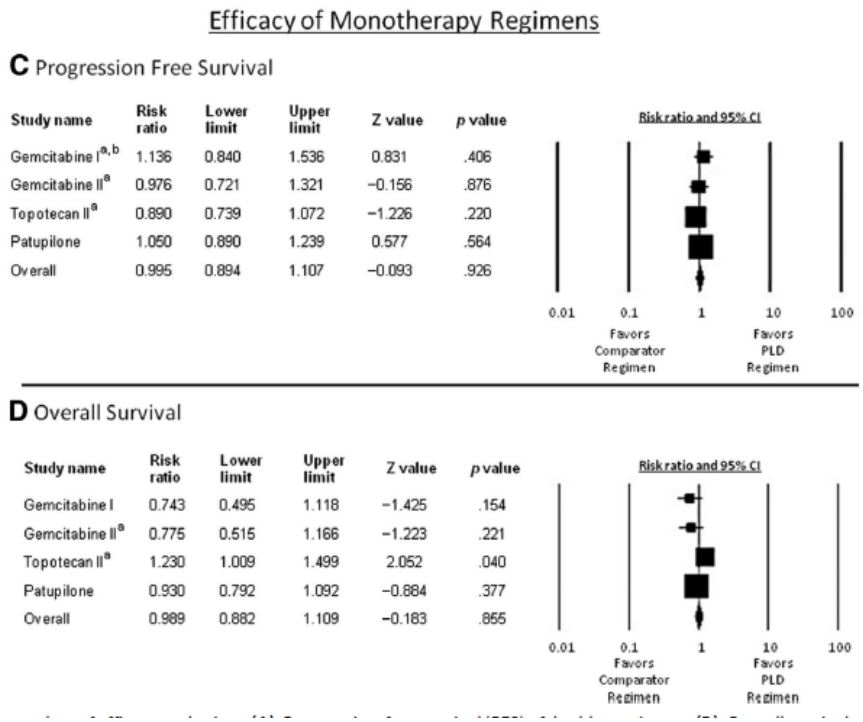


Adverse events

- Meta-analysis showed that C+PLD was associated with a decreased risk of an allergic reaction (RR, 0.43; 95% CI, 0.26–0.71; p<.001) and neutropenia (RR, 0.84; 95% CI, 0.76 – 0.93; p < .001) compared with C+P.
- C+PLD was associated with an increased risk of anemia (RR, 1.96;95% CI, 1.37–2.79; p<.001) and thrombocytopenia (RR, 3.44;95% CI, 2.45– 4.84; p<.001), which are other indices of myelosuppression in conjunction with neutropenia.
- Grade 2 or higher toxicities: C+PLD was associated with an increased risk of mucositis/ stomatitis (RR, 2.48; 95% CI, 1.76 –3.51; p<.001), gastrointestinal [GI] toxicity (RR, 1.16; 95% CI, 1.09 –1.23; p <.001), and cutaneous toxicity (RR, 5.6; 95% CI, 3.43– 8.81; p<.001).

Monotherapy

- The meta-analysis showed no difference in PFS (4 RCTs, HR, 0.99; 95% CI, 0.89 –1.11; p=0.93) or OS (4 RCTs, HR, 0.99;95%CI, 0.88 –1.11; p= .86) between single-agent PLD and other monotherapy regimens
- PLD was associated with a decreased risk of neutropenia (RR, 2.37;95%CI, 1.90 –2.95; p<.001), anemia (RR, 1.85;95% CI, 1.34 –2.54; p.001), thrombocytopenia (RR, 3.52; 95% CI, 2.02– 6.16; p<.001), and GI toxicity (RR, 1.81; 95% CI, 1.53–2.14; p<.001) compared with the comparator regimens
- PLD was also associated with an increased risk of mucositis/ stomatitis (RR, 0.10; 95% CI, 0.04–0.26; p .001) compared with the other monotherapies .
- The incidence of hand-foot syndrome in PLD-treated groups ranged from 5.5% to 37.5%. There were no cases of hand-foot syndrome I any comparator therapies.



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Anmerkung/Fazit der Autoren

The findings of our analysis support C+PLD as a possible alternative to C+P for ovarian cancer, with similar efficacy in both regimens. Because the side effect profiles of the two regimens are drastically different, the choice of regimen could reasonably be based on individual patient preference to avoid certain side effects. In the recurrent or refractory setting where platinum resistance is likely to exist, there is similar efficacy among the monotherapy agents, but PLD may be more tolerable.

Kommentare zum Review

- Poolen von Studien zum platinsensitivem bzw. platinresistentem Karzinom und Studien zur Erst- und ≥2-Linie

3.4 Leitlinien

National Comprehensive Cancer Network (NCCN), 2018 [11].

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.

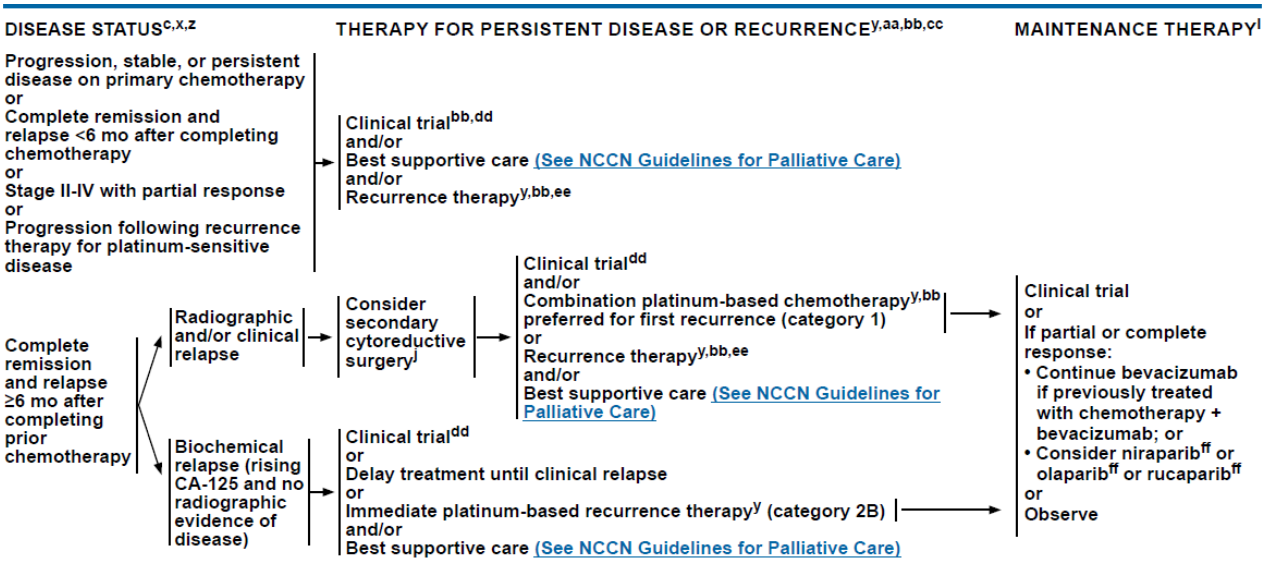
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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.
[j] 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 Recurrence Therapies for Epithelial (including LCOH[j])/Fallopian Tube/Primary Peritoneal Cancer[k]

	Cytotoxic Therapy (In alphabetical order)*		Targeted Therapy*
	Platinum-Sensitive Disease[l,m]	Platinum-Resistant Disease	Single Agents
Preferred Agents	Carboplatin/gemcitabine[2] Carboplatin/gemcitabine/bevacizumab[n,o,p,3] Carboplatin/liposomal doxorubicin[4] Carboplatin/paclitaxel[5] Carboplatin/paclitaxel/bevacizumab[l,n,o,p,6] Cisplatin/gemcitabine[7]	Docetaxel[8] Etoposide, oral[9] Gemcitabine[10,11] Liposomal doxorubicin[10,11] Liposomal doxorubicin/bevacizumab[n,o,12] Paclitaxel (weekly)[13] ± pazopanib[14] Paclitaxel (weekly)/bevacizumab[n,o,12] Topotecan[15,16] Topotecan/bevacizumab[n,o,12]	Bevacizumab[n,o,17,18] Olaparib[q,19] Rucaparib[r,20]

*NOTE: For LCOH, all regimens are category 2A unless indicated.

Other Potentially Active Recurrence Therapies on OV-B (6 of 10)

Useful in Certain Circumstances Recurrence Therapies on OV-B (7 of 10)

[j] Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[k] Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and fallopian tube. Int J Gyn Ca 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.
[l] In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[m] Platinum-based combination therapy should be considered for platinum-sensitive recurrences.
[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.
[p] If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARP inhibitor.
[q] For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with three or more lines of chemotherapy.
[r] For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.

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

	Regimens (In alphabetical order)[a,l]	Recommended Use
Useful in Certain Circumstances	5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[n,o]	Mucinous carcinoma
	Capecitabine + oxaliplatin ± bevacizumab (category 2B for bevacizumab)[n,o]	Mucinous carcinoma
	Carboplatin/paclitaxel, albumin bound (platinum-sensitive disease)	Paclitaxel, albumin bound may be substituted for taxane for confirmed hypersensitivity
	Carboplatin/paclitaxel[t]	Elderly patients (> age 70) with platinum-sensitive disease
	Pembrolizumab[25]	Microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors[u]

Continued

Preferred Recurrence Therapies on OV-B (5 of 10)

Other Potentially Active Recurrence Therapies on OV-B (6 of 10)

[a]See Discussion for references.
[j]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[k]Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and Fallopian tube. Int J Gyn Ca 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.
[l]In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[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.
[t]For recommended dosing for elderly patients, see OV-B (2 of 10).
[u]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.

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.

Fotopoulou C et al., 2017 [2].

British Gynaecological Cancer Society (BGCS)

Epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice

Leitlinienorganisation/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.

Methodik

Grundlage der Leitlinie

Systematische Suche und Bewertung der Literatur (SIGN-Systematik), informale Konsensusverfahren, externes Reviewverfahren.

Recherche/Suchzeitraum:

- up to August 2014

LoE

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

GoR

A At least one meta-analysis, systematic reviews or RCT's rated as 1++ and directly applicable to the patient population or

A systematic review of RCTs or a body of studies rated as 1+ directly applicable to the patient population and demonstrating consistency of results.

B Evidence from Level 2++ studies directly applicable to the patient population or extrapolated from level 1 studies.

C Evidence from Level 2+ studies directly applicable to the patient population or extrapolated evidence from studies rated at 2++.

D Evidence from Level 3 or 4 studies or extrapolated evidence from studies rated as 2+.

Sonstige methodische Hinweise

- Repräsentativität der Leitliniengruppe unklar
- Auswahl der Literatur unklar, finanzielle Unabhängigkeit unklar
- Interessenkonflikte unklar

Empfehlungen

Table 1
The Gynecologic Cancer Intergroup (GCIG) [162] categorisation of patients based on the length of remission following platinum-based chemotherapy. The platinum-free interval is however somewhat theoretical and in real-life exists as a spectrum.

Classification	Definition
Platinum sensitive (PS)	Progress with an interval of >12 months after completion of chemotherapy
Partially PS (pPS)	Progress with an interval of between 6–12 months after completion of chemotherapy
Platinum resistant (PR)	Progress with an interval of less than 6 months after completion of chemotherapy
Platinum refractory (PRef)	Progress during, or within 4 weeks after completion of chemotherapy

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/gemcitabine 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 platinumresistant 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 chemotherapy 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 outcomes in a carefully selected population [115]. If the patient cannot tolerate chemotherapy 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].

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Leitlinienprogramm Onkologie, 2017 [6,7].

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.

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9.2.1. Rezidivtherapie, wenn eine Platin-haltige-Therapie keine Option ist (ehemals platin-resistentes Rezidiv)

8.2.	Evidenzbasiertes Statement	2016
Level of Evidence 1+	Eine Kombinationschemotherapie bietet keinen Vorteil gegenüber einer Monotherapie.	
	Leitlinien: NHS TA91 [357] Primärstudien: [422, 423, 425, 432-439]	

8.3.	Evidenzbasiertes Statement	2013
Level of Evidence 1+	Endokrine Therapien sind einer Monochemotherapie unterlegen.	
	Leitlinien: NHS TA91 [357] Primärstudien: [422, 423, 425, 432-439]	

8.4.	Evidenzbasierte Empfehlung	2013
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 [357] Primärstudien: [422, 423, 425, 432-439]	

8.5.	Evidenzbasierte Empfehlung	2016
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: [440]	

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 [425]. Bei taxannaiven Patientinnen zeigen Topotecan und Paclitaxel ähnliche Wirksamkeit [423, 433]. Gemcitabin wurde in 2 Studien im Vergleich zu pegyliertem liposomalem Doxorubicin untersucht. Beide Studien waren als Überlegenheitsstudien gegenüber pegyliertem liposomalem Doxorubcin geplant und verfehlten ihren primären Endpunkt, beide Substanzen scheinen jedoch ähnlich aktiv zu sein [435, 436]. Eine Alkylantientherapie mit Treosulfan oder Canfosfamide war einer Therapie mit Topotecan bzw. pegyliertem liposomalem Doxorubicin unterlegen [432, 441]. Bisher konnte kein Effektivitätsvorteil für eine Kombinationschemotherapie bei platinresistentem Rezidiv aufgezeigt werden [438]. Chemotherapien sind bzgl. des PFS effektiver als endokrine Therapien.

Dies gilt z. B. für die Vergleiche von Treosulfan mit Leuprorelin, sowie Tamoxifen mit pegyliertem liposomalem Doxorubicin oder Paclitaxel [422, 423, 425, 432-438, 442, 443]. Es gibt Hinweise auf eine Verlängerung des progressionsfreien Intervalls durch die Addition von Bevacizumab zu einer Chemotherapie mit pegyliertem liposomalen Doxorubicin, Topotecan oder Paclitaxel [444]. 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 [445].

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

8.6.	Konsensbasierte Empfehlung	2013
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/Bevacizumab* • Carboplatin/pegyliertes liposomales Doxorubicin • Carboplatin/Paclitaxel • Carboplatin/Gemcitabin *bei Patientinnen mit erstem Rezidiv und ohne vorherige VEGF gerichtete Therapie	

Durch die Addition von Bevacizumab zu einer Chemotherapie bestehend aus Carboplatin/Gemcitabin [446, 447] oder Carboplatin/Paclitaxel [448] konnte das progressionsfreie Überleben und die Ansprechrate gegenüber der alleinigen Chemotherapie deutlich verbessert werden aber nicht das Gesamtüberleben. Daten zur Lebensqualität liegen in diesen Studien jedoch nicht vor (Stand 8/17: 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 [424] und Carboplatin/Gemcitabin [449] 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 [450].

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 [451].

Des Weiteren wurde im Rahmen der AGO-OVAR-2.22/NOVA-Studie (NCT01847274) der Effekt von Niraparib 300 mg/d als Erhaltungstherapie nach erfolgreicher platinbasierter Chemotherapie untersucht [452]. Es zeigte sich hierbei ein deutlicher (HR in den drei Subgruppen: 0,27, 0,38, 0,45) signifikanter Unterschied zugunsten einer Erhaltungstherapie bzgl. des PFS mit Niraparib 300 mg/d unabhängig vom BRCA-Status bzw. auch unabhängig von der durchgeführten Testung auf Homologe Rekombinationsdeffizienz des Tumors (Stand 8/17: derzeit nicht zugelassen, Bearbeitung durch die Leitliniengruppe erfolgt voraussichtlich in 2018).

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 [455]. In dieser Subgruppe konnte bisher allerdings keine Überlegenheit einer Nicht-Platinhaltigen Therapie (pegyliertes liposomales Doxorubicin) im Vergleich zu einer platinhaltigen Therapie aufgezeigt werden [456]. 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.

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Francis J et al., 2017 [3].

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

Chemotherapy for patients with platinum-sensitive recurrent ovarian cancer:

- If the option to participate in a clinical trial is not available, combination platinumbased chemotherapy should be considered, providing that there are no contraindications. 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.

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].

2. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, 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):3323-9.

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10. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2007;25 (19):2811-8.

<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.

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].

<u>Interpretation of Evidence for Recommendation</u>

- 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).

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.

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.

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.

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.

Scottish Intercollegiate Guidelines Network (SIGN), 2013 [13].

Management of epithelial ovarian cancer

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

repräsentative Leitliniengruppe, CoI jährlich dargelegt, Entwicklungsprozess folgt der Systematik der evidenzbasierten Medizin, öffentliche und fachbezogene Konsultation,

Recherche/Suchzeitraum:

- 2003 bis 2012

LoE

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

GoR

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

Sonstige methodische Hinweise

- *Suche und Auswahl der Literatur nicht vollständig dargelegt*

- *CoI nur auf Anfrage einsehbar*
- *Ableitung der Empfehlungen und Konsensprozesse unklar*

Empfehlungen

6.3.1 systemic therapy in recurrent ovarian cancer

Women with platinum-sensitive relapsed ovarian cancer should be treated with a platinum based combination with paclitaxel, PLDH or gemcitabine. GOR A

LoE: 1+ bis 1++

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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]

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Anhang

Gibson JM et al., 2013 [4]. The Role of Pegylated Liposomal Doxorubicin in Ovarian Cancer: A Meta-Analysis of Randomized Clinical Trials

Studiencharakteristika

Trial or cohort (year published)	Treatment	No. of patients	Type of trial	Age (years)	Patient characteristics	Pretreatment status	Outcomes reported
CALYPSO [19] (2012)	C+P C+PLD	509 467	Randomized, multicenter, phase III	61 60.5	Platinum-sensitive ovarian carcinoma, fallopian tube carcinoma, and extraovarian papillary serous tumor	Disease progression after first- or second-line platinum- and taxane-based chemotherapy	PFS, toxicity, QOL, OS
MITO-2 [9] (2011)	C+P C+PLD	410 410	Randomized, multicenter, phase III	57 57	Platinum-sensitive epithelial ovarian carcinoma	Chemotherapy naïve	PFS, OS, treatment activity, toxicity, QOL
Hellenic [10] (2010)	C+P C+PLD	96 93	Randomized, multicenter, phase II	63 62	Platinum-sensitive recurrent ovarian carcinoma	One cycle or more of platinum-based chemotherapy	Relative risk and toxicity, TTP, OS
Gemcitabine I [16] (2008)	Gemcitabine PLD	77 76	Randomized, multicenter, phase III	63 63	Platinum-sensitive recurrent epithelial ovarian carcinoma	Failed first-line platinum/paclitaxel chemotherapy	TTP, OS, response rate, toxicity, QOL
Gemcitabine II [21] (2007)	Gemcitabine PLD	99 96	Randomized, multicenter, phase III	59 62	Platinum-resistant epithelial ovarian carcinoma, fallopian tube carcinoma, primary peritoneal carcinoma	Prior platinum-based chemotherapy required, ≤2 prior regimens allowed	PFS, tumor response, time to treatment failure, OS, QOL
Topotecan I [22][a] (2009)	Topotecan PLD	87 130	Randomized, multicenter, phase III	NR NR	Platinum-resistant advanced epithelial ovarian carcinoma, fallopian tube carcinoma, peritoneal carcinoma	Failed one second-line therapy with either topotecan or PLD	Toxicity[b]
Topotecan II [13] (2004)	Topotecan PLD	239 235	Randomized, multicenter, phase III	60 60	Mixed platinum sensitivity with recurrent epithelial ovarian carcinoma	Failed first-line, platinum-based chemotherapy	PFS, OS, response rate, duration of response, toxicity
Canfosfamide [22][a] (2009)	Canfosfamide PLD	231 130	Randomized, multicenter, phase III	60 NR	Platinum-resistant advanced epithelial ovarian carcinoma, fallopian tube carcinoma, peritoneal carcinoma	Failed one second-line therapy with either topotecan or PLD	Toxicity[b]
Patupilone [15] (2012)	Patupilone PLD	412 417	Randomized, multicenter, phase III	59 59	Platinum-resistant epithelial ovarian carcinoma, primary fallopian tube carcinoma, primary peritoneal carcinoma	Failed ≥4 cycles of platinum-based chemotherapy or discontinued because of toxicity	OS, PFS, objective response rate, duration of response, cancer antigen 125, response, toxicity

[a]Canfosfamide and Topotecan I are two cohorts of the same trial comparing canfosfamide with PLD or topotecan.
[b]PFS and OS were also reported, but the hazard ratios were based on canfosfamide versus PLD or topotecan; therefore, these results were not included in this meta-analysis.
Abbreviations: C+P, carboplatin and paclitaxel; C+PLD, carboplatin and pegylated liposomal doxorubicin; PLD, pegylated liposomal doxorubicin; NR, not recorded; PFS, progression free survival; QOL, quality of life; OS, overall survival; TTP, time to progression.