Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

## Vorgang: 2017-B-136 Olaparib

Stand: September 2017

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

**Olaparib**
**[Erhaltungstherapie des platinsensitiven Rezidivs eines Ovarialkarzinoms, Eileiterkarzinoms oder Peritonealkarzinoms]**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
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| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *Siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“* |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | *Keine* |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Olaparib (Beschluss über die Nutzenbewertung vom 26. November 2015) – seröses epitheliales Ovarialkarzinom, Eileiterkarzinom oder primäres Peritonealkarzinom |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | *Siehe systematische Literaturrecherche* |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
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| Zu bewertendes Arzneimittel: | |
| Olaparib<br>L01XX46<br>Lynparza™ | <u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u><br>Olaparib wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem platinsensitiven Rezidiv eines high-grade epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die auf eine platinbasierte Chemotherapie ansprechen (vollständiges oder partielles Ansprechen). |
| Bevacizumab<br>L01XC07<br>Avastin® | Bevacizumab wird in Kombination mit Carboplatin und Gemcitabin oder in Kombination mit Carboplatin und Paclitaxel zur Behandlung von erwachsenen Patienten mit einem ersten platinsensitiven Rezidiv eines epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die zuvor noch nicht mit Bevacizumab oder mit anderen VEGF-Inhibitoren bzw. auf den VEGF-Rezeptor zielenden Substanzen behandelt wurden.<br>(Stand: Juni 2017) |
| Carboplatin<br>L01XA02<br>Carboplatin Kabi | Carboplatin wird verwendet für die Behandlung von fortgeschrittenem epithelialem Ovarialkarzinom als:<br>• Second-Line Therapie, wenn eine andere Behandlung nicht erfolgreich war.<br>(Stand: Dezember 2016) |
| Cisplatin<br>L01XA01<br>Cisplatin Teva® | Cisplatin Teva® wird angewendet zur Behandlung des:<br>• fortgeschrittenen oder metastasierten Ovarialkarzinoms<br>(Stand: Mai 2016) |
| Cyclophosphamid<br>L01AA01<br>Endoxan® | Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt:<br>- Fortgeschrittenes Ovarialkarzinom<br>(Stand: Januar 2015) |
| Doxorubicin<br>L01DB<br>Ribodoxo® | Fortgeschrittenes Ovarialkarzinom<br>(Stand: Februar 2017) |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| Doxorubicin *(liposomal)*<br>L01DB01<br>Caelyx® | Caelyx ist indiziert:<br>Zur Behandlung von Patientinnen mit fortgeschrittenem Ovarialkarzinom nach Versagen einer platinhaltigen First-Line-Chemotherapie.<br>(Stand: April 2016) |
| Epirubicin<br>L01DB03<br>Epimedac® | Epirubicin wird zur Behandlung folgender neoplastischer Erkrankungen eingesetzt:<br>• fortgeschrittenes Ovarialkarzinom<br>(Stand: Juli 2016) |
| Etoposid<br>L01CB01<br>Vepesid® | In der Monotherapie ist Vepesid K angezeigt zur palliativen systemischen Behandlung fortgeschrittener Ovarialkarzinome nach Versagen von platinhaltigen Standardtherapien.<br>(Stand: September 2015) |
| Gemcitabin<br>L01BCO5<br>Gemedac® | Gemcitabin ist in Kombination mit Carboplatin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem epithelialen Ovarialkarzinom, bei Patientinnen mit einem Rezidiv nach einer rezidivfreien Zeit von mindestens 6 Monaten nach einer platinbasierten Erstlinientherapie angezeigt.<br>(Stand: Februar 2017) |
| Melphalan<br>L01AA03<br>Alkeran | Fortgeschrittenes Ovarialkarzinom nach Versagen der Standardtherapie.<br>(Stand: Januar 2017) |
| Olaparib<br>L01XX46<br>Lynparza™ | Lynparza wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines BRCA-mutierten (Keimbahn und/oder somatisch) high-grade serösen epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die auf eine Platin-basierte Chemotherapie ansprechen (vollständiges oder partielles Ansprechen).<br>(Stand: Dezember 2016) |
| Paclitaxel<br>L01CD01<br>Paclitaxel-GRY® | Zur Second-line-Chemotherapie des Ovarialkarzinoms ist Paclitaxel-GRY® bei Patientinnen mit metastasierendem Ovarialkarzinom nach Versagen einer Standardtherapie mit platinhaltigen Arzneimitteln angezeigt.<br>(Stand: Dezember 2016) |
| Topotecan<br>L01XX17<br>Hycamtin® | Als Monotherapie ist Topotecan angezeigt zur Behandlung von:<br>• Patientinnen mit metastasierendem Ovarialkarzinom nach Versagen einer Primär oder Folgetherapie.<br>(Stand: April 2015) |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

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| Trabectedin<br>L01CX01<br>Yondelis® | Yondelis in Kombination mit pegyliertem liposomalem Doxorubicin (PLD) ist indiziert für die Behandlung von Patientinnen mit einem platinsensiblen Ovarialkarzinomrezidiv.<br>(Stand: Juli 2016) |
| Treosulfan<br>L01AB02<br>Ovastat® | Ovastat 1000 (5000) mg ist allein oder in der Kombination mit anderen antineoplastisch wirksamen Substanzen angezeigt in der palliativen Therapie epithelialer Ovarialkarzinome der FIGO Stadien II – IV. Eine Therapie mit Treosulfan allein (Monotherapie) ist angezeigt, wenn eine Kontraindikation gegen Cisplatin besteht. In allen anderen Fällen sollte Treosulfan mit Cisplatin kombiniert werden.<br>(Stand: Juni 2014) |

Quellen: AMIS-Datenbank, Fachinformationen

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

**Inhalt**



## Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Ovarialkarzinom, Eileiterkarzinom oder primärem Peritonealkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.06.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, 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 1300 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.

**Indikation:**

Als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines high-grade epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms, die auf eine platinbasierte Chemotherapie ansprechen.

Abkürzungen:

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| (S)AE/(S)UE | (schwerwiegendes) unerwünschtes Ereignis |
| Akdae | Arzneimittelkommission der deutschen Ärzteschaft |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CCO | Cancer Care Ontario |
| CI/KI | Konfidenzintervall |
| DAHTA | Deutsche Agentur für Health Technology Assessment |
| DRKS | Deutsches Register Klinischer Studien |
| ESMO | European Society for Medical Oncology |
| FIGO | International Federation of Gynecology and Obstetrics |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| HR | Hazard ration |
| ICTRP | International Clinical Trials Registry Platform |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NGC | National Guideline Clearinghouse |
| NHS CRD | National Health Services Center for Reviews and Dissemination |
| NICE | National Institute for Health and Care Excellence |
| OS | Gesamtüberleben |
| PFS | Progressionsfreies Überleben |
| ROC | rezidiviertes Ovarialkarzinom |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

**IQWiG-Berichte/G-BA-Beschlüsse**

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| **G-BA, 2015 [4].**<br><br>Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Olaparib, vom 27. November 2015 | **Zugelassenes Anwendungsgebiet:**<br>Olaparib (Lynparza™) wird als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines BRCA-mutierten (Keimbahn und/oder somatisch) high-grade serösen epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms angewendet, die auf eine Platin-basierte Chemotherapie ansprechen (vollständiges oder partielles Ansprechen).<br>**1. Ausmaß des Zusatznutzens des Arzneimittels**<br>Olaparib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 gilt der medizinische Zusatznutzen durch die Zulassung als belegt.<br>Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien.<br>**Ausmaß des Zusatznutzens:**<br>Nicht quantifizierbar |

**Cochrane Reviews**

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| **Lawrie TA et al., 2013 [5].**<br>Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer | 1. Fragestellung<br>To evaluate the efficacy and safety of PLD (Pegylated liposomal doxorubicin) in women with relapsed EOC (epithelial ovarian cancer). |
| | 2. Methodik<br>**Population:** Women with relapsed EOC of any stage, including patients with both platinum-sensitive and platinum-resistant disease.<br>**Intervention:**<br>1. PLD in combination with platinum-based therapy versus platinum-based therapy with another agent, e.g. PLD plus carboplatin versus paclitaxel (PAC) plus carboplatin.<br>2. Other chemotherapy agent(s) versus PLD, e.g. topotecan (TOP) versus PLD.<br>3. PLD plus other agent(s) versus PLD alone or with placebo, e.g. trabectedin (TBD) plus PLD versus PLD.<br>**Endpunkte:** PFS, OS, severe adverse events, Quality of life (QoL), symptom control<br>**Suchzeitraum:** 1990 until February 2013<br>**Anzahl eingeschlossene Studien:** 14 RCTs<br>**Qualitätsbewertung der Studien:** Cochrane Collaboration's tool (selection bias, performance bias, attrition bias, reporting bias, other possible sources of bias), judged by three categories for each study: low risk (+), unclear risk (?) or high risk (-) of bias.<br>**Heterogenität:** We assessed statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$ and $Chi^2$ statistics and 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.<br>**Publikationsbias:** There was an insufficient number of included studies to adequately evaluate the potential for small study effects, such as publication bias, using funnel plots |
| | 3. Ergebnisdarstellung<br>**Risk of bias**<br>• Allocation: Most studies weremulticentre studies with central randomisation and treatment allocation after registrationwith the organising centre, andwere therefore at a lowrisk of selection bias.<br>• Blinding: All of the included studies were open-label, i.e. the participants and attending healthcare professionals were aware of |

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| | 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.<br>• 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).<br>• 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.<br>**PLD plus carboplatin versus carboplatin ± other drug/s (platinsensitives Rezidiv)**<br><u>Overall survival</u><br>• 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).<br><u>Safety and adverse events</u><br>• ***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).<br>• ***PLD/carbo versusPAC/carbo***: Women receiving the PLD/carboregimen were statistically significantly more likely than those receiving the PAC/carbo regimen to experience the following: anaemia (grade 3 to 4): two studies,1140 participants; risk ratio (RR) 1.59, 95% CI 1.02 to 2.50; $I^2$ = 0%; P value 0.04); and thrombocytopenia (grade 3 to 4): two studies, 1140 participants; RR 2.69, 95% CI 1.83 to 3.96; $I^2$ = 0%; P <0.00001.<br>They were also statistically significantly less likely to experience the following: alopecia (grade 2): two studies, 1140 participants; RR 0.09, 95% CI 0.06 to 0.15; $I^2$ = 44%; P < 0.00001; neuropathy (grade 3 to 4): two studies, 1140 participants; RR 0.20, 95% CI 0.08 to 0.50; $I^2$ = 0%; P value 0.0005; arthralgia/myalgia (grade 3 to 4): two studies, 1140 participants; RR 0.12, 95% CI 0.02 to 0.67; $I^2$ = 0%; P value 0.02; and hypersensitivity reactions (HSRs; grade 3 to |

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| | 4): two studies, 1140 participants; RR 0.29, 95% CI 0.15 to 0.54; $I^2$ = 0%; P value 0.0001<br>• 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).<br><u>Quality of life</u><br>• 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%).<br>**Other drug(s) versus PLD**<br><u>Overall survival</u><br>• 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.<br>• 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.<br>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).<br>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).<br>• 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)** |

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| | Safety and adverse events<br><br>The statistically significant differences between interventions with regard to G3 to 4 severe adverse events were as follows (by subgroup):<br><br>*GEM versus PLD (two studies; 338 women):*<br><br>• hand-foot syndrome, RR 0.07 (95% CI 0.01 to 0.54) in favour of GEM(Analysis 2.3);<br><br>• neutropenia, RR 2.25 (95% CI 1.46 to 3.47) in favour of PLD (Analysis 2.5).<br><br>*TOP versus PLD (one study; 474 women):*<br><br>• hand-foot syndrome, RR 0.01 (95% CI 0.00 to 0.15) in favour of TOP (Analysis 2.3);<br>• stomatitis, RR 0.05 (95% CI 0.01 to 0.38) in favour of TOP (Analysis 2.4);<br>• anaemia, RR 5.16 (95% CI 2.93 to 9.10) in favour of PLD (Analysis 2.6);<br>• neutropenia, RR 6.31 (95% CI 4.46 to 8.94) in favour of PLD (Analysis 2.5);<br>• thrombocytopenia, RR 27.12 (95% CI 8.69 to 84.67) in favour of PLD (Analysis 2.7);<br>• alopecia, RR 4.75 (95% CI 1.38 to 16.30) in favour of PLD (Analysis 2.11).<br><br>**PLD plus other drug/s versus PLD alone (platinresistent and -sensitive)**<br><br>Overall survival<br><br>• 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).<br><br>• 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)<br><br>• 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. |
| | 4. Anmerkungen/Fazit der Autoren<br><br>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 |

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| | 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**.<br>*5. Kommentar zum Review*<br>• *In den Studien ohne platinbasierte Therapieschemen (TOP vs. PLD und GEM vs PLD) sind teilweise platinresistente und –sensitive Frauen eingeschlossen*<br>• *UEs in der Gesamtpopulation untersucht*<br>• *Patupilone nicht zugelassen* |
| **Wiggans AJ et al., 2015 [16].**<br>Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer | 1. Fragestellung<br>To determine the benefits and risks of PARP inhibitors for the treatment of epithelial ovarian cancer (EOC). |
| | 2. Methodik<br>**Population:** Women ≥ 18 years old with histologically proven EOC of any stage.We excluded women with other concurrent malignancies.<br>**Intervention/Komparator:**<br>• DNA-repair pathway inhibitors versus no treatment<br>• DNA-repair pathway inhibitors + conventional chemotherapy versus conventional chemotherapy<br>• DNA-repair pathway inhibitors versus conventional chemotherapy<br>**Endpunkte:** Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), Quality of life, adverse events:<br>**Suchzeitraum**: 1990 to April 2015.<br>**Anzahl eingeschlossene Studien:** 4 RCTs involving 599 women with EOC (3 zu Olaparib)<br>**Qualitätsbewertung der Studien**: Cochrane Collaboration's tool (selection bias, performance bias, attrition bias, reporting bias, other possible sources of bias), judged by three categories for each study: low risk (+), unclear risk (?) or high risk (-) of bias.<br>**Heterogenität:** We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).<br>**Publikationsbias:** We did not produce funnel plots corresponding to meta-analysis due to the limited number of included studies. |

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| | 3. Ergebnisdarstellung<br><br>**Risk of bias**<br><br>• We considered studies to be at a low (Ledermann 2012) to moderate (Oza 2015) risk of bias (risk mainly due to lack of blinding).<br><br>**Overall survival**<br><br>***PARP inhibitor versus placebo (as maintenance) / PARP inhibitor plus conventional chemotherapy versus conventional chemotherapy alone***<br><br>• 2 studies (426 participants) compared Olaparib versus placebo (Ledermann 2012) or conventional chemotherapy (Oza 2015).<br><br>• There was no significant difference in OS when we pooled data from the two studies that included participants with platinum sensitive disease (HR1.05, 95%CI 0.79 to 1.39; $I^2$ = 0%). We graded this evidence as moderate quality using the GRADE approach.<br><br>• Ledermann 2012: Arm 1: OLA 400 mg bd maintenance therapy; Arm 2: Placebo tablets bd **maintenance therapy**.<br>All women within 8 weeks after completion of the last dose of platinum-based chemotherapy.<br><br>• Oza 2015: Arm A - OLA orally in combination with paclitaxel (P) intravenous (IV) and carboplatin (C); followed by OLA monotherapy maintenance; Arm B - Paclitaxel (P) IV and carboplatin (C) IV; followed by a post-completion phase in which no study treatment was administered.<br><br>***PARP inhibitor versus conventional chemotherapy***<br><br>• One study (Kaye 2012) compared olaparib to conventional chemotherapy (pegylated liposomal doxorubicin (PLD))<br><br>• Ninety-seven women with EOC who had relapsed within 12 months of platinum-based chemotherapy (i.e. platinum-resistant and partially platinum-sensitive disease) were randomised to one of three treatment arms (olaparib200mg, olaparib 400mg, PLD50mg) in a ratio of 1:1:1.<br><br>• HR 0.82 (80%CI 0.52 to 1.31) (in favour of olaparib).<br><br>**Adverse events/QoL**<br><br>• Olaparib was associated with more severe adverse events (G3/4) during the maintenance phase compared with controls (risk ratio (RR) 1.74, 95% CI 1.22 to 2.49; 385 participants, two studies; high quality evidence).<br><br>• Quality of life data were insufficient for meta-analysis. |

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| | 4. Anmerkungen/Fazit der Autoren<br><br>PARP inhibitors appear to improve PFS in women with recurrent platinum-sensitive disease. Ongoing studies are likely to provide more information about whether the improvement in PFS leads to any change in OS in this subgroup of women with EOC. More research is needed to determine whether PARP inhibitors have any role to play in platinum-resistant disease.<br><br>*5. Kommentar zum Review*<br>• *Olaparib als Monotherapie für die Erhaltungstherapie von erwachsenen Patientinnen mit einem Platin-sensitiven Rezidiv eines BRCA-mutierten (Keimbahn und/oder somatisch) high-grade serösen epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms zugelassen, die auf eine Platin-basierte Chemotherapie ansprechen (vollständiges oder partielles Ansprechen)*<br>• *In Kaye 2012 auch platinresistente Frauen eingeschlossen*<br>• *eine weitere Studien zu Veliparib hier nicht dargestellt wegen fehlender Zulassung* |

**Systematische Reviews**

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| **Wu YS et al., 2017 [17].**<br>Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials | 1. Fragestellung<br>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. |
| | 2. Methodik<br>Population: women with ovarian cancer<br>Intervention: chemotherapy plus bevacizumab<br>Komparator: chemotherapy alone<br>Endpunkt: efficacy and safety (PFS, OS, ORR and incidence of adverse events)<br>Studiendesign: randomized controlled trial<br>Suchzeitraum: from database inception to May 2016<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 5/4 994<br>Qualitätsbewertung der Studien: Cochrane Collaboration's tool, judged by three categories for each study: low risk (+), unclear risk (?) or high risk (-) of bias<br>Heterogenität: Chi squared test and Cochran Q-test used, I2 > 75% indicated considerable heterogeneity<br>Publikationsbias: Due to the small quantity of included trials ( < 10), we did not examine potential publication bias with Begg and Egger tests. |
| | 3. Ergebnisdarstellung<br>• data of outcomes were summarized in Table 2 (siehe Anhang)<br>• overall risk of bias was judged to be low, risk of bias was unclear in the study that was published in an abstract form (GOG213)<br>• OCEANS und GOG2013 mit platinsensitiven Rezidiven<br>• AURELIA platinresistente Rezidive<br>**Overall Survival**<br>• fixed effect model used<br>• Bevacizumab significantly better OS <u>in the recurrent setting</u> (HR 0.87, 95% CI 0.77-0.99, I2 = 0%)<br>**Adverse events**<br>• fixed effect model used<br>• among this updated analysis, the risks were significantly increased as follows: |

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| | • Hypertension (risk ratio (RR) 21.27, 95% CI 9.42-48.02, I2 = 0%),<br>• proteinuria (RR 4.77, 95% CI 2.15-10.61, I2 = 0%),<br>• wound healing disruption (RR 3.55, 95% CI 1.09-11.59, I2 = 0%),<br>• bleeding (RR 3.16, 95% CI 1.59-6.30, I2 = 0%),<br>• GI perforations (RR 2.76, 95% CI 1.51-5.03, I2 = 0%),<br>• arterial thrombosis events (RR 2.39, 95% CI 1.39-4.10, I2 = 14%),<br>• and venous thrombosis events (RR 1.43, 95% CI 1.04-1.96, I2 = 39%) |
| | 4. Anmerkungen/Fazit der Autoren<br><br>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. … ORR is improved in overall population by the addition of bevacizumab.<br><br>5. *Kommentar zum Review:*<br>• *platinresistente und –sensitive Karzinome zusammen analysiert*<br>• *UEs für die Gesamtpopulation analysiert*<br>• *This work was supported by the National Key Clinical Specialist Construction Programs of China ([2013] NO. 544).*<br>• *All authors claimed no competing interests.* |
| **Edwards SJ et al., 2015 [2].**<br><br>Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent or refractory ovarian cancer: a systematic review and economic evaluation | 1. Fragestellung<br><br>To determine the comparative clinical effectiveness and cost-effectiveness of topotecan (Hycamtin®, GlaxoSmithKline), pegylated liposomal doxorubicin hydrochloride (PLDH; Caelyx®, Schering-Plough), paclitaxel (Taxol®, Bristol-Myers Squibb), trabectedin (Yondelis®, PharmaMar) and gemcitabine (Gemzar®, Eli Lilly and Company) for the treatment of advanced, recurrent ovarian cancer. |
| | 2. Methodik<br><br>Population: People with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy<br><br>Intervention: For people with platinum-sensitive ovarian cancer:<br>• paclitaxel as monotherapy or in combination with platinum-based chemotherapy<br>• PLDH as monotherapy or in combination with platinum-based chemotherapy<br>• gemcitabine in combination with carboplatin<br>• trabectedin in combination with PLDH |

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| | • topotecan monotherapy<br><br>Komparator: For people with platinum-sensitive ovarian cancer:<br><br>• the interventions listed above in comparison with each other<br>• bevacizumab in combination with platinum-containing chemotherapy (subject to NICE appraisal)<br>• single-agent platinum chemotherapy<br><br>Endpunkte: overall survival (OS); progression-free survival (PFS); overall response rate; health-related quality of life (HRQoL); and adverse effects of treatment<br><br>Suchzeitraum: from inception to May 2013<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 16/5 368<br><br>Qualitätsbewertung der eingeschlossenen Studien: according to recommendations by the NHS CRD and Cochrane Handbook for Systematic Reviews of Interventions and recorded using the Cochrane risk of bias tool |
| | 3. Ergebnisdarstellung<br><br>• five studies evaluated the intervention and comparator within their licensed indication, and dose and route of administration (table 8, siehe Anhang)<br>• 11 RCTs evaluated the intervention or comparator outside the parameters specified in the licence, in terms of, for example, dose or route of administration<br><br>**Overall survival (platinum-sensitive recurrent ovarian cancer)**<br><br>• 10 RCTs evaluating 8 different head-to-head comparisons of interventions and comparators of interest were identified (Table 11, siehe Anhang).<br>• For the outcome OS, of the combination **platinum-based treatments** compared with platinum monotherapy, significant gains in OS were observed for paclitaxel plus platinum compared with platinum monotherapy:<br>o The trial carried out by Gonzalez-Martin et al. was a Phase II trial of a 'pick-the-winner' design, which the authors state has a '90% chance of selecting the better treatment if the difference is at least 15% and the smaller response rate is assumed to be 30%'. Therefore, no sample size calculation was carried out. A 'pick-the-winner' trial is designed as a screening trial to facilitate a selection between promising experimental regimens in a Phase II setting, and, as such, do not typically include the standard of care. Trials with a 'pick the winner' design are underpowered for hypothesis testing or comparisons of treatment effect on the outcomes of interest, such as survival. Therefore, as the authors comment, all reported statistical analyses are exploratory and reported p-values should be interpreted with caution. Limited details on trial methodology are reported and the level of masking in the trial is unclear. Although it is reported that randomisation was carried out in a central data centre, the method of randomisation is not described. |

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| | o ICON4 and AGO-OVAR 2.2 are well-conducted parallel trials. Comprehensive details on most aspects of trial methodology are provided in the full publication. The level of masking is unclear but OS is the primary outcome and therefore awareness of treatment allocation is unlikely to influence results of this outcome. Analyses of clinical effectiveness are based on the ITT population.<br>• **non-platinum-based treatments:** difference in OS between treatment groups was not statistically significant in any trial<br>**Overall survival (fully platinum-sensitive ovarian cancer)**<br>• 3 of the 4 trials reported a HR as a measure of treatment effect (Table 14, siehe Anhang)<br>• difference between treatment groups not statistically significant in any trial<br>**Overall survival (partial platinum sensitivity)**<br>• PLDH monotherapy has been found to significantly prolong OS compared with topotecan (Table 15, siehe Anhang):<br>o The trial carried out by Gordon et al. was generally a well-designed trial. Although open label in design, scans for assessment of disease response and progression underwent independent radiological review. Although the methods state that analyses are based on the ITT principle, in the first publication, results are based on patients who received at least a partial dose of study drug (474 patients out of 481 randomised), which is a modified ITT analysis. However, in the publication describing longer-term follow-up of OS, analysis of OS is based on the 'all randomised' population and, as such, is a true ITT analysis.<br>• trabectedin plus PLDH has been found to be significantly more effective than PLDH alone at increasing OS<br>o The OVA-301 trial was a well-conducted trial. Methodologically, the design of the trial was robust, with clinical effectiveness analyses based on the ITT population, and progression and response reviewed by an independent radiologist who was masked to treatment allocation. A secondary analysis of the primary outcome of PFS was carried out based on review by an independent oncologist (radiological assessment in conjunction with prespecified clinical data) who was also masked to treatment allocation. The methods of the trial are well reported. As noted in the Final Appraisal Determination (FAD) for the assessment of trabectedin plus PLDH as part of the Technology Appraisal process (TA222),73 one potential area that affects the external validity of the trial is the omission of a platinum-based chemotherapy as a comparator, particularly as a large proportion of patients enrolled had platinum-sensitive disease. The authors commented that the inclusion of platinum-resistant patients contributed to the decision against use of a platinum-based control, as platinum-based therapy would have been inappropriate in this setting.<br>**Quality of Life (full population)**<br>• 10 of the 16 RCTs reported data on QoL<br>• reporting of QoL was minimal in most studies<br>• majority of studies presenting a narrative description of changes in QoL rather than absolute changes in QoL score<br>• HRQoL reporting in ovarian cancer trials show considerable disparity in the level of reporting of QoL results, the questionnaires used to evaluate QoL, and the time points for evaluation |

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| | • difference between treatment groups not statistically significant in any of the “within licensed indication” trials<br><br>**Adverse effcts (full population)**<br><br>• commonly occurring adverse effects: alopecia, nausea and vomiting, haematological toxicities (neutropenia, anaemia, thrombocytopenia and leucopenia)<br>• severe (grades 3 and 4) effects: allergic reaction; alopecia; anaemia; fatigue; febrile neutropenia; nausea and vomiting; and neuropathy<br>• no chemotherapy was consistently associated with either a lower risk or a higher risk of the severe adverse events |
| | 4. Anmerkungen/Fazit der Autoren<br><br>For people with platinum-sensitive disease who receive treatment with platinum-based therapies, paclitaxel plus platinum could be considered cost-effective compared with platinum at a threshold of £30,000 per additional QALY. For people with platinum-sensitive disease and treated with non-platinum-based therapies, it is unclear whether PLDH would be considered cost-effective compared with paclitaxel at a threshold of £30,000 per additional QALY; trabectedin plus PLDH is unlikely to be considered cost-effective compared with PLDH. For PRR patients, it is unlikely that topotecan would be considered cost-effective compared with PLDH.<br><br>5. *Kommentar zum Review*<br>• *Ergebnisse der Netzwerkmetaanalysen wegen fehlender Ähnlichkeit und hoher Heterogenität der Studien nicht dargestellt*<br>• *Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.* |
| **Ding SS et al., 2014 [1].**<br><br>Systematic evaluation of bevacizumab in recurrent ovarian cancer treatment | 1. Fragestellung<br><br>This study aimed to evaluate the efficacy and safety of bevacizumab in the treatment of recurrent ovarian cancer. |
| | 2. Methodik<br><br>The Cochrane Library, MEDLINE, and EMBASE were searched. Data regarding the use of bevacizumab in recurrent ovarian cancer were collected from randomized controlled trials (RCTs). Data were evaluated with the Cochrane systematic method, and statistical analysis was performed with the RevMan 5.2 software. |
| | 3. Ergebnisdarstellung<br><br>Two RCTs comprising a total of 845 patients were included. |

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| | Bevacizumab combined with conventional chemotherapy prolonged the progression-free survival (PFS) (hazard ratio [HR] 0.48; 95% confidence interval [CI], 0.41–0.56), without significantly altering the overall survival (OS) (HR 1.03; 95% CI 0.79–1.33). Adverse events (NCI-CTCAE v.4.0) associated with bevacizumab were ≥ grade 3 hypertension (relative risk [RR] 2.30; 95% CI 1.39–3.83) and bleeding (RR 4.76; 95% CI 1.38–16.37). |
| | 4. Anmerkungen/Fazit der Autoren:<br><br>Bevacizumab prolonged the PFS of patients with recurrent ovarian cancer. Additional high-quality randomized controlled trials are needed to verify these results.<br><br>5. *Kommentar zum Review*<br>• *hier Kurzextraktion wegen aktuellerer Daten (siehe oben)*<br>• *je eine Studie mit platinresistenten und eine mit platinsensitiven Frauen in Metaanalyse eingeschlossen*<br>• *This paper was supported by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (2011211A038).* |
| **Zhou M et al., 2013 [19].**<br><br>Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis | 1. Fragestellung<br><br>Platinum-based standard chemotherapy improves survival of ovarian cancer (OC), but the five-year survival rate remains below 50%. Antiangiogenic agents (7.5 or 15 mg/kg Bevacizumab, Bev) plus to standard chemotherapy improve progression-free survival (PFS) not overall survival (OS) in completed randomized controlled trials (RCTs). The efficacy and safety of two doses of Bev + standard chemotherapy remain controversial. |
| | 2. Methodik<br><br>MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane databases and ClinicalTrials.gov were searched. The outcomes of eligible RCTs included PFS, OS and toxicities. Hazard ratio (HR) and relative risk (RR) were used for the meta-analysis and were expressed with 95% confidence intervals (CIs). |
| | 3. Ergebnisdarstellung<br><br>Bev + chemotherapy improved PFS (HR, 0.48; 95% CI, 0.41 to 0.57; P = .000) in recurrent OC (2 trials, 845 patients).<br><br>OCEANS found no significant difference in HR for OS between two groups (HR: 1.03, CI: 0.79 to 1.33; P > 0.05). As the OS endpoint was not achieved until now in AURELIA, we could not pool HRs of OS in recurrent OC.<br><br>Bev + chemotherapy increased<br>• non-CNS bleeding (RR, 3.63; 95% CI, 1.81 to 7.29; P = .000), |

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| | • hypertension grade ≥ 2 (RR, 4.90; 95% CI, 3.83 to 6.25; P = .000),<br>• arterial thromboembolism (RR, 2.29; 95% CI, 1.33 to 3.94; P = .003),<br>• gastrointestinal perforation (RR, 2.90; 95% CI, 1.44 to 5.82; P = .003), and<br>• proteinuria grade ≥ 3 (RR, 6.63; 95% CI 3.17 to 13.88; P = .000).<br><br>No difference was observed between the two Bev doses in PFS (HR, 1.04; 95% CI, 0.88 to 1.24) or OS (HR, 1.15, 95% CI, 0.88 to 1.50), but 15 mg/kg Bev increased toxicities. |
| | 4. Anmerkungen/Fazit der Autoren:<br><br>Bev + standard chemotherapy delayed progression for newly diagnosed and recurrent OC, and improved survival for newly diagnosed OC. The 7.5 mg/kg dose appeared to be optimal for newly diagnosed OC patients with high risk for progression.<br><br>5. *Kommentar zum Review*<br>• *hier Kurzextraktion wegen aktuellerer Daten (siehe oben)*<br>• *für „recurrend OC" je eine Studie mit platinresistenten und eine mit platinsensitiven Frauen in Metaanalyse eingeschlossen*<br>• *This study was supported by the Educational Commission of Liaoning Province of China (No. 20060973), the Science and Technology Planning Project of Liaoning Province of China (No. 2007225009-1, 2011404013-9, 2011225019), and the National Natural Science Foundation of China (No. 81372532). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*<br>• *The authors have declared that no competing interests exist.* |
| **Ye Q et al., 2013 [18].**<br><br>Bevacizumab in the treatment of ovarian cancer: a meta-analysis from four phase III randomized controlled trials | 1. Fragestellung<br><br>The aim of this meta-analysis was to summarize the efficacy and safety of bevacizumab in the treatment of ovarian cancer. |
| | 2. Methodik<br><br>We sought to identify randomised controlled trials (RCTs) by searching PubMed and Web of Science. Outcomes were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events. |
| | 3. Ergebnisdarstellung<br><br>Four studies with 4,246 patients were included. Combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in ORR (OR 2.165, 95 % CI 1.511–3.103) and in PFS (HR 0.691, 95 % CI 0.517–0.865), compared with chemotherapy alone. |

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| | There was no evidence of a significant improvement in OS (HR 0.934, 95 % CI 0.826–1.041).<br><br>The subgroup analysis based on patient inclusion criteria showed that the addition of bevacizumab to standard chemotherapy for ovarian cancer was not associated with a significant improvement in OS, either as a first-line therapy (HR = 0.916, 95 % CI 0.799–1.033), or in patients with recurrent ovarian cancer (HR = 1.027, 95 % CI 0.757–1.296).<br><br>It also had significantly increased risk of gastrointestinal events (OR 2.743, 95 % CI 1.580–4.763; P\0.001), hypertension (OR 4.630, 95 % CI 3.737 to 5.737; P\0.001), proteinuria (OR 4.872, 95 % CI 2.617–9.069; P\0.001), and arterial thromboembolism (OR 1.994, 95 % CI 1.210–3.286; P = 0.007). |
| | 4. Anmerkungen/Fazit der Autoren:<br><br>This meta-analysis suggests that the addition of bevacizumab to chemotherapy offers meaningful improvement in objective response rate and progression free survival in ovarian cancer treatment, but does not benefit overall survival. It also significantly increased the occurrence of gastrointestinal events, hypertension, proteinuria, and arterial thromboembolism.<br><br>5. *Kommentar zum Review*<br>• *hier Kurzextraktion wegen aktuellerer Daten (siehe oben)*<br>• *für „recurrend OC" je eine Studie mit platinresistenten und eine mit platinsensitiven Frauen in Metaanalyse eingeschlossen*<br>• *The authors have declared no conflicts of interest.* |
| **Raja FA et al., 2013 [14].**<br><br>Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data | 1. Fragestellung<br><br>The benefit of platinum-based combination chemotherapy in randomized trials varies, and a meta-analysis was carried out to gain more secure information on the size of the benefit of this treatment. |
| | 2. Methodik<br><br>Population: relapsed platinum-sensitive ovarian cancer<br><br>Intervention: single-agent platinum chemotherapy<br><br>Komparator: platinum-based combinations<br><br>Endpunkte: OS (primary), PFS (secondary)<br><br>Suchzeitraum: bis 2012<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 4/1 300<br><br>Qualitätsbewertung der eingeschlossenen Studien: checked using standardized checks listed below and reviewing the trial protocols and published papers (… including checks for missing values and data validity and consistency across variables. To assess the randomization |

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| | integrity, we looked for unusual patterns in the sequencing of allocation or imbalances in the number of patients who are randomized to each treatment arm. Follow-up of surviving patients was also assessed to ensure that it was balanced by treatment arm and as up-to-date as possible)<br><br>Heterogenitätsanalysen: χ2 heterogeneity tests and the I2 statistic for inconsistency |
| | 3. Ergebnisdarstellung:<br>• median follow-up of 36.1 months<br>• further characteristics in table 1 (siehe Anhang)<br><br>**Overall survival (OS) analyses**<br><br>• based on 865 deaths from four trials<br>• demonstrated evidence for the benefit of combination-platinum chemotherapy (HR = 0.80; 95% CI, 0.64–1.00; P = 0.05) with moderate, but non-significant, heterogeneity among the trials (P = 0.14; I2 = 45%)<br>• no evidence of a difference in the relative effect of combination-platinum chemotherapy on OS <u>in patient subgroups</u> defined by<br>o previous paclitaxel (Taxol) treatment (OS, P = 0.49; PFS, P = 0.66),<br>o duration of treatment-free interval (OS, P = 0.86; PFS, P = 0.48) or<br>o number of previous lines of chemotherapy (OS, P = 0.21; PFS, P = 0.27) |
| | 4. Anmerkungen/Fazit der Autoren:<br><br>In this individual patient data (IPD) meta-analysis, we have demonstrated that combination-platinum chemotherapy improves OS and PFS across all subgroups. This provides the strongest evidence to date of the benefit of combination-platinum over single-agent platinum.<br><br>5. *Kommentar zum Review*<br>• *auch Frauen mit FIGO Stadium I in den Studien eingeschlossen*<br>• *FAR and NC are supported by Cancer Research UK. Grant C444/A4125.*<br>• *The authors have declared no conflicts of interest.* |

**Leitlinien**

<table>
<tr><td rowspan="3">National Comprehensive Cancer Network (NCCN), 2017 [8].<br><br>Ovarian cancer including fallopian tube cancer and primary peritoneal cancer</td><td>Fragestellung/Zielsetzung: nicht formuliert</td></tr>
<tr><td>Methodik<br><br>Grundlage der Leitlinie: systematische Literatursuche<br><br>Suchzeitraum (jährliche Aktualisierungen): 1.9.2014 – 1.10.2015<br><br>LoE/ GoR:<br><br>NCCN Categories of Evidence and Consensus<br><br>Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.<br><br>Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.<br><br>Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.<br><br>Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.<br><br>All recommendations are category 2A unless otherwise noted.<br><br>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</td></tr>
<tr><td>Freitext/Empfehlungen/Hinweise</td></tr>
</table>

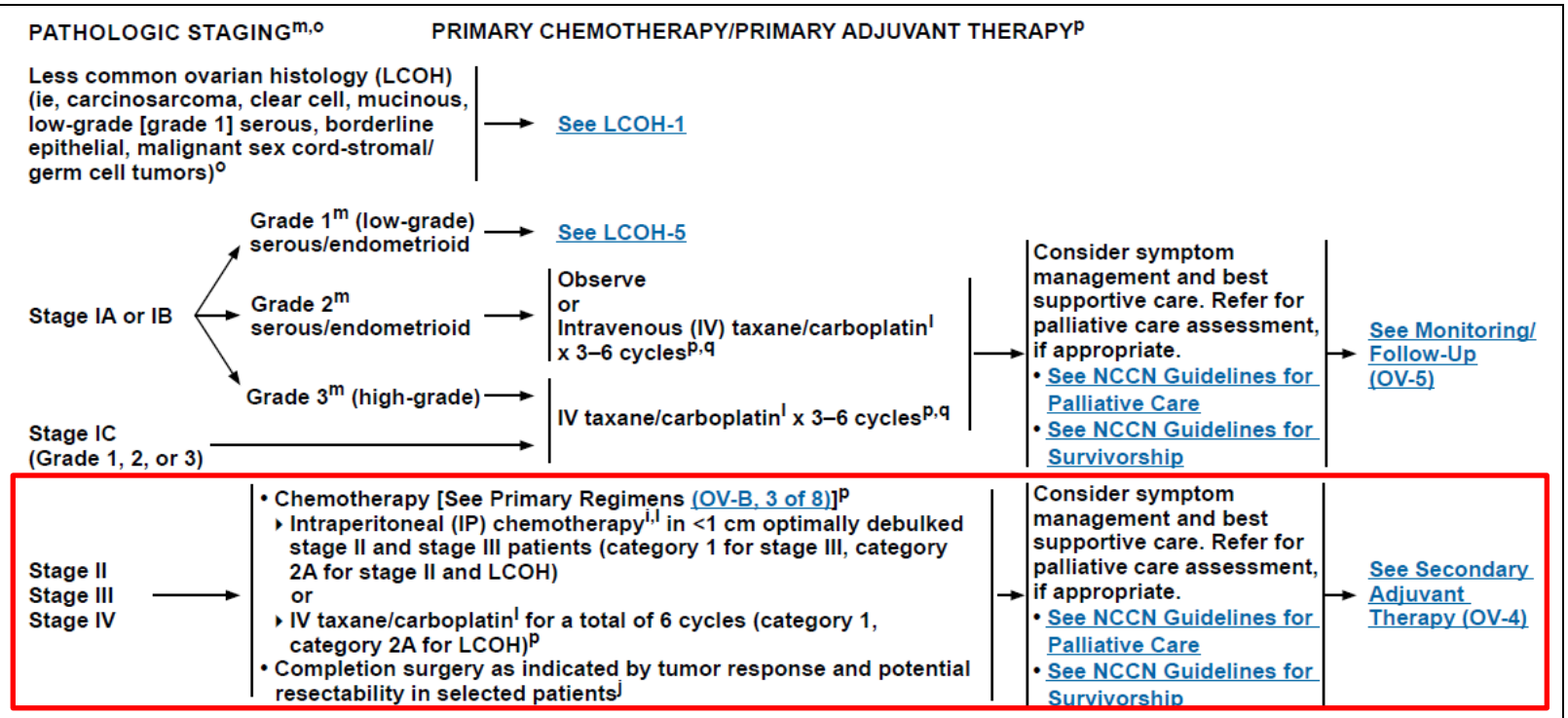
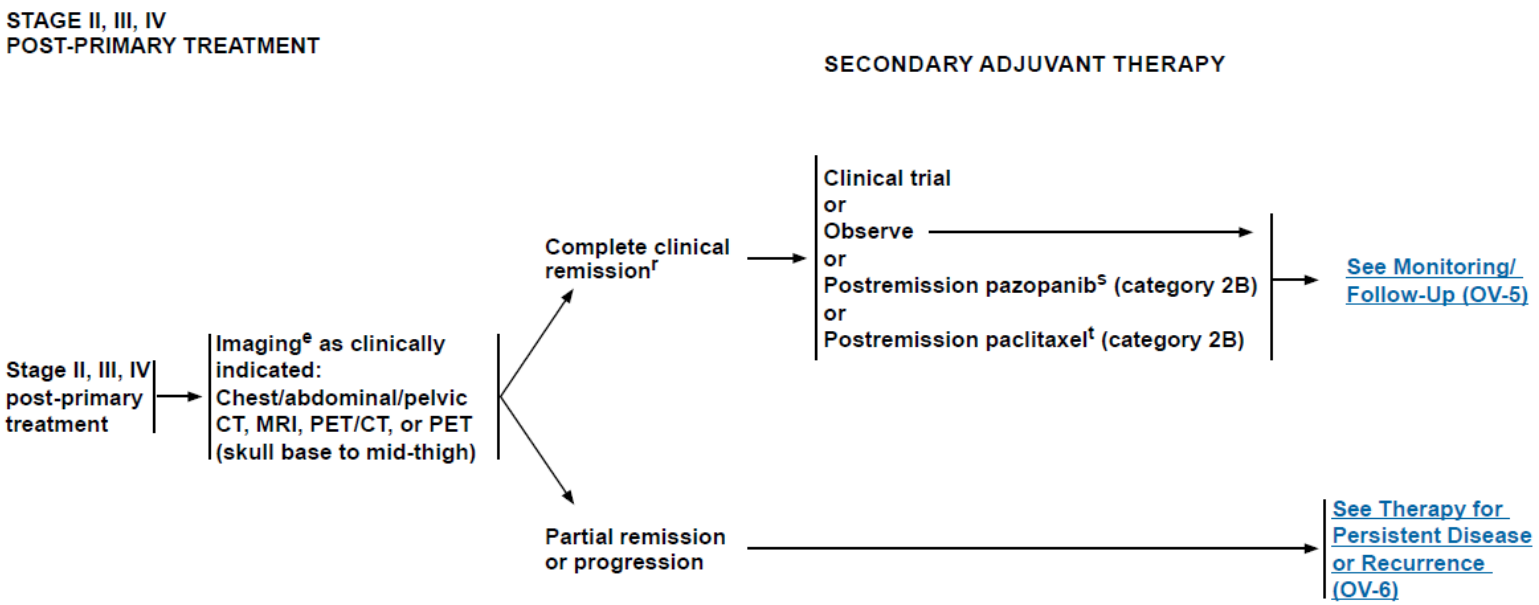
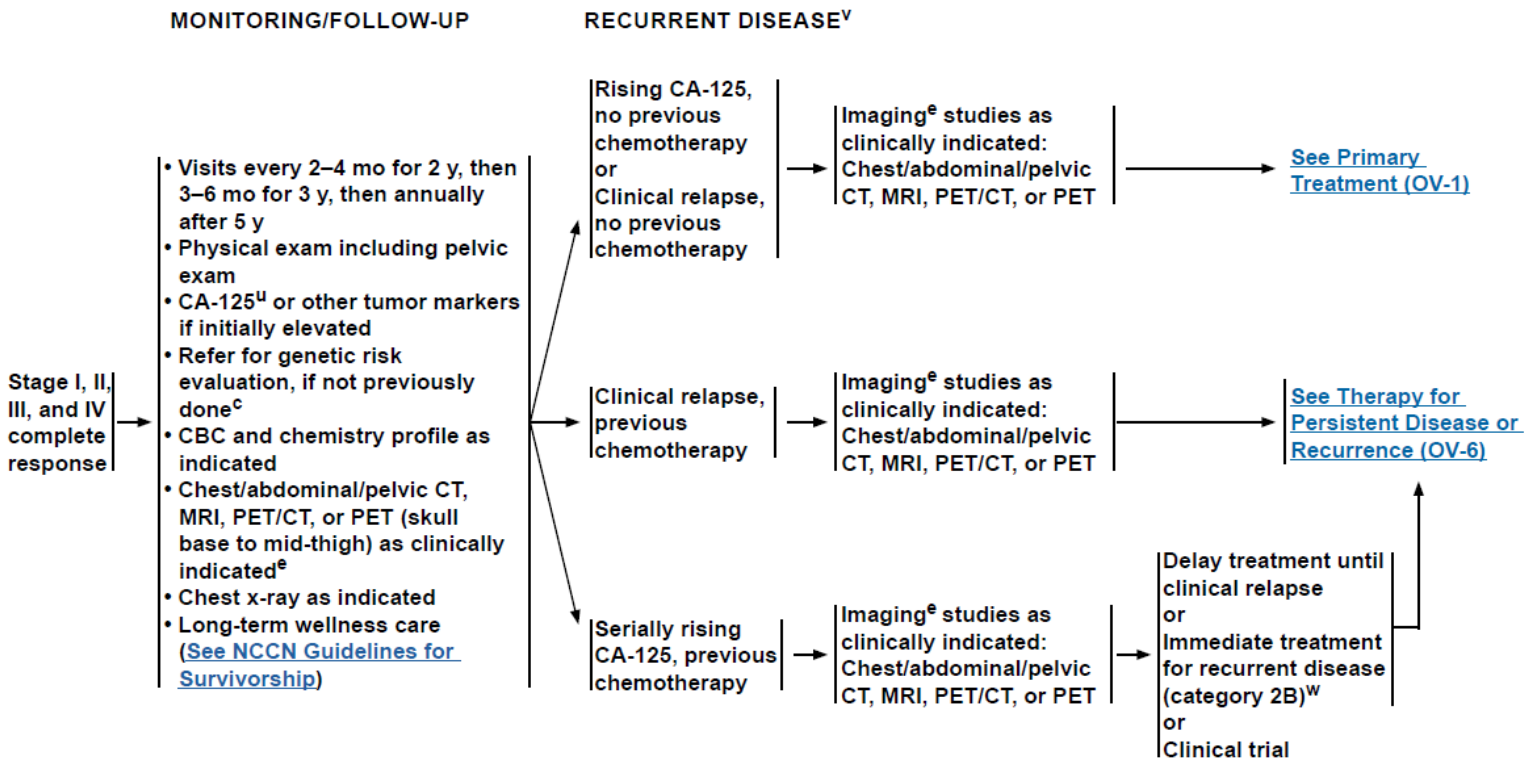



**Abbildung 1: OV-3**



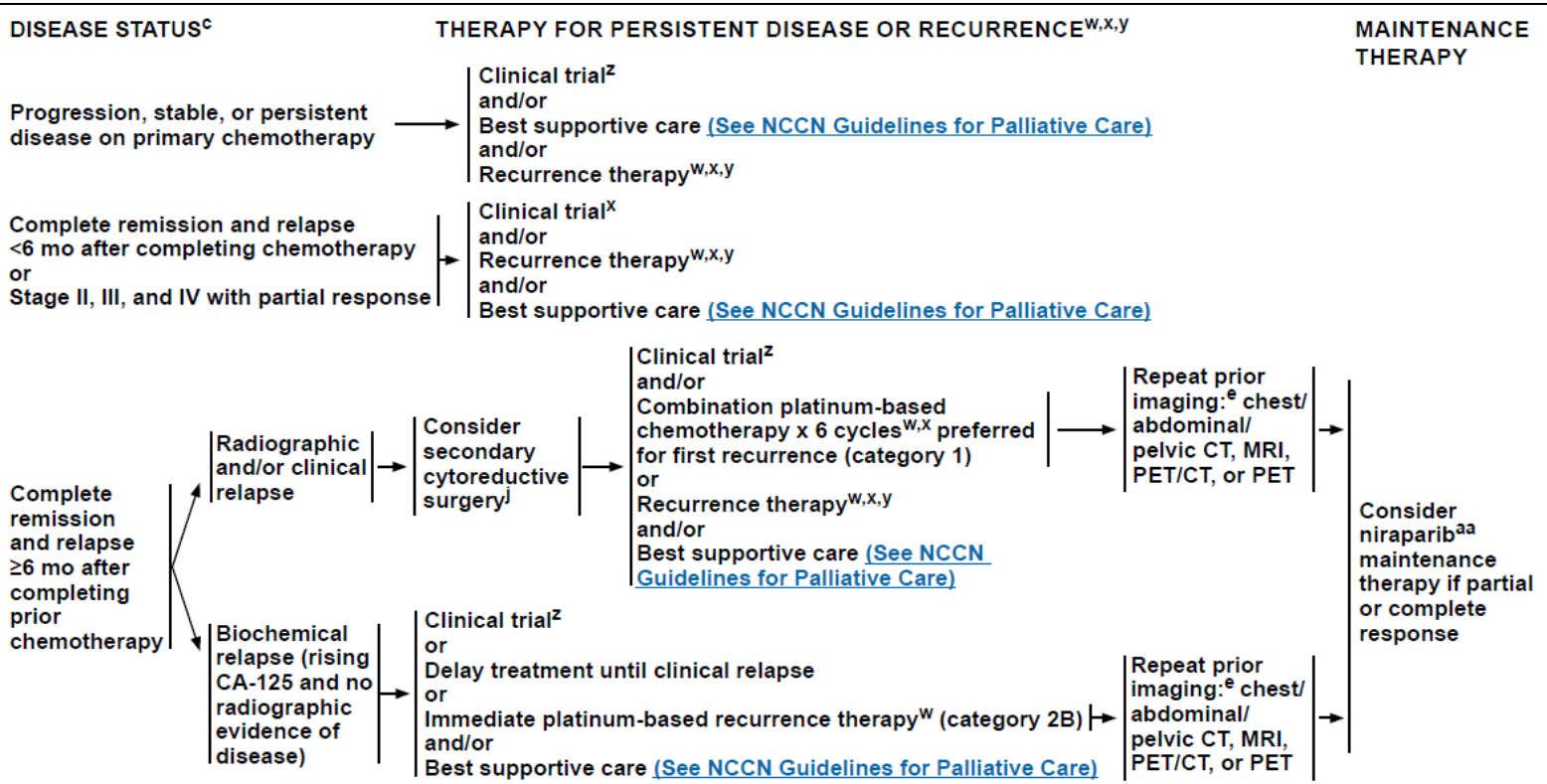

[e]Imaging performed with contrast unless contraindicated.
[r]No definitive evidence of disease.
[s]There is limited evidence that postremission pazopanib may be less effective in east Asian women with ovarian cancer. (Kim JW, Mahner S, Wu LY, et al. Pazopanib maintenance therapy in East Asian women with advanced epithelial ovarian cancer: results from AGO-OVAR16 and an East Asian study. Int J Gynecol Cancer 2015.)
[t]See Discussion for dosing.

**Abbildung 2: OV-4**




[c]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[e]Imaging performed with contrast unless contraindicated.
[u]There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See The Society of Gynecologic Oncology (SGO) position statement and Discussion.
[v]Consider symptom management and best supportive care. See NCCN Guidelines for Palliative Care. Refer for palliative care assessement, if appropriate.
[w]See Acceptable Recurrence Therapies (OV-B, 5 of 8).

**Abbildung 3: OV-5**




[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[e] Imaging performed with contrast unless contraindicated.
[j] See Principles of Surgery (OV-A).
[w] See Acceptable Recurrence Therapies (OV-B, 5 of 8).
[x] 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.
[y] See Ancillary Palliative Surgical Procedures in Principles of Surgery (OV-A 4 of 4).
[z] Clinical trials with newer agents should be strongly considered.
[aa] For those with platinum-sensitive disease who have completed two or more lines of platinum-based therapy.

**Abbildung 4: OV-6**

**PRINCIPLES OF SYSTEMIC THERAPY (5 of 8)**
**Acceptable Recurrence Therapies for Epithelial (including LCOH[g])/Fallopian Tube/Primary Peritoneal Cancer[h]**

| | Cytotoxic Therapy (In alphabetical order)* | | Targeted Therapy* |
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| Preferred Agents | **Platinum-Sensitive Disease[i,j]**<br>Carboplatin[1]<br>Carboplatin/docetaxel[2,3]<br>Carboplatin/gemcitabine[1]<br>Carboplatin/gemcitabine/bevacizumab[k,l,m,4]<br>Carboplatin/liposomal doxorubicin[5] (category 1)<br>Carboplatin/paclitaxel, albumin bound (for patients with confirmed taxane hypersensitivity)<br>Carboplatin/paclitaxel (category 1)[6]<br>Carboplatin/paclitaxel (weekly)[7]<br>Cisplatin[6]<br>Cisplatin/gemcitabine[8]<br><br>**Additional options for mucinous carcinoma only:**<br>5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,l]<br>Capecitabine + oxaliplatin | **Platinum-Resistant Disease**<br>Docetaxel[9]<br>Etoposide, oral[10]<br>Gemcitabine[11,12]<br>Liposomal doxorubicin[11,12]<br>Liposomal doxorubicin/bevacizumab[k,l,13]<br>Paclitaxel (weekly)[14] ± pazopanib[15]<br>Paclitaxel (weekly)/bevacizumab[k,l,13]<br>Topotecan[16,17]<br>Topotecan/bevacizumab[k,l,13] | **Single Agents**<br>Bevacizumab[k,l,18,19]<br>Olaparib[n,20,21]<br>Rucaparib[o,24] (platinum-resistant disease) |

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

Other Potentially Active Agents on OV-B (6 of 8)

[g]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[h]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.
[i]In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[j]Platinum-based combination therapy should be considered for platinum-sensitive recurrences.
[k]There are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients previously treated with bevacizumab.
[l]Contraindicated for patients at increased risk of GI perforation.
[m]If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity.
[n]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.
[o]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.

**Abbildung 5: OV-B**

**PRINCIPLES OF SYSTEMIC THERAPY (6 of 8)**
**Acceptable Recurrence Therapies for Epithelial (including LCOH[g])/Fallopian Tube/Primary Peritoneal[h]**

| | Cytotoxic Therapy (In alphabetical order)* | Hormonal Therapy* | Targeted Therapy* | Radiation Therapy* |
|---|---|---|---|---|
| Other Potentially Active Agents | Single Agents[p,22]<br>Altretamine<br>Capecitabine<br>Cyclophosphamide<br>Doxorubicin<br>Ifosfamide<br>Irinotecan<br>Melphalan<br>Oxaliplatin<br>Paclitaxel<br>Paclitaxel, albumin bound<br>Pemetrexed<br>Vinorelbine<br><br>Combinations<br>Carboplatin/paclitaxel/bevacizumab[i,k,l,m] (platinum-sensitive disease) | Aromatase inhibitors<br>Leuprolide acetate<br>Megestrol acetate<br>Tamoxifen | Pazopanib (category 2B)[23]<br>Rucaparib[o,24] (platinum-sensitive disease) | Palliative localized radiation therapy |

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

Continued

[g]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[h]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.
[i]In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[k]There are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients previously treated with bevacizumab.
[l]Contraindicated for patients at increased risk of GI perforation.
[m]If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity.
[o]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.
[p]Many of these agents have not been tested in patients who have been treated with modern chemotherapy regimens.

**Abbildung 6: OV-B**

**PRINCIPLES OF SYSTEMIC THERAPY (8 of 8)**
**REFERENCES FOR ACCEPTABLE RECURRENCE THERAPIES**


[1]Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699-4707.

[2]Strauss HG, Henze A, Teichmann A, et al. Phase II trial of docetaxel and carboplatin in recurrent platinum-sensitive ovarian, peritoneal and tubal cancer. Gynecol Oncol 2007;104:612-616.

[3]Kushner DM, Connor JP, Sanchez F, et al. Weekly docetaxel and carboplatin for recurrent ovarian and peritoneal cancer: a phase II trial. Gynecol Oncol 2007;105:358-364.

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[8]Rose PG. Gemcitabine reverses platinum resistance in platinum-resistant ovarian and peritoneal carcinoma. Int J Gynecol Cancer 2005;15:18-22.

[9]Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2003;88:130-135.

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[11]Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007;25:2811-2818.

[12]Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol 2008;26:890-896.

[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(13):1302-1308.

[14]Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436-440.

[15]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 randomised, open-label, phase 2 trial. Lancet Oncol 2015;16:561-568.

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[19]Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180-5186.

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**Abbildung 7: OV-B**

Leitlinien Fortsetzung:

<table>
<tr><td rowspan="3">Fotopoulou C et al., 2017 [3].<br><br>British Gynaecological Cancer Society (BGCS)<br><br>Epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice</td><td>Zielsetzung:<br><br>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.</td></tr>
<tr><td>Methodik<br><br>Grundlage der Leitlinie: systematische Suche und Bewertung der Literatur (SIGN-Systematik), informale Konsensusverfahren, externes Reviewverfahren,<br><br>Suchzeitraum: up to August 2014<br><br>LoE:<br><br>1++ High quality meta analyses, systematic reviews of RCTs or RCTs with a very low risk of bias<br><br>1+ Well conducted meta analyses, systematic reviews of RCTs or RCTs with a low risk of bias<br><br>1– Meta analyses, systematic reviews of RCTs or RCTs with a high risk of bias<br><br>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<br><br>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<br><br>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<br><br>3 Non-analytical studies e.g. case reports, case series<br><br>4 Expert opinion<br><br>GoR:<br><br>A At least one meta-analysis, systematic reviews or RCT's rated as 1++ and directly applicable to the patient population or<br><br>A systematic review of RCTs or a body of studies rated as 1+ directly applicable to the patient population and demonstrating consistency of results.<br><br>B Evidence from Level 2++ studies directly applicable to the patient population or extrapolated from level 1 studies.<br><br>C Evidence from Level 2+ studies directly applicable to the patient population or extrapolated evidence from studies rated at 2++.<br><br>D Evidence from Level 3 or 4 studies or extrapolated evidence from studies rated as 2+.<br><br>Sonstige methodische Hinweise: Repräsentativität der Leitliniengruppe unklar, Auswahl der Literatur unklar, finanzielle Unabhängigkeit unklar, Interessenkonflikte unklar</td></tr>
<tr><td>Freitext/Empfehlungen/Hinweise</td></tr>
</table>

*Management of recurrent disease*

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)**

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 |


[96] Hall M, Rustin G. Recurrent ovarian cancer: when and how to treat. Curr Oncol Rep 2011;13(December (6))459–71

[107] Blackledge G, et al. Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer 1989;59(April (4)) 650–3

[108] Stuart GC, et al. Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer 2011;21(May (4))750–5

[109] Wilson MK, et al. 5th ovarian cancer consensus conference of the gynecologic cancer intergroup: recurrent disease. Ann Oncol 2016(December)

[110] Tanguay JS, et al. Epithelial ovarian cancer: role of pegylated liposomal Doxorubicin in prolonging the platinum-free interval and cancer antigen 125 trends during treatment. Int J Gynecol Cancer 2009;19(April (3))361–6

[111] Colombo N. Efficacy of trabectedin in platinum-sensitive-relapsed ovarian cancer: new data from the randomized OVA-301 study. Int J Gynecol Cancer 2011;21(May (Suppl. 1))S12–6

[112] Lawrie TA, et al. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer. Cochrane Database Syst Rev 2013;09(July (7))CD006910

[113] Raja FA, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. Ann Oncol 2013;24(December (12))3028–34

[114] Aghajanian C, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30(June (17))2039–45

[115] Pujade-Lauraine E, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32(May (13))1302–8

<table>
<tr><td></td><td>[116] Kokka F, et al. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev 2010;08(December (12))CD007926<br><br>[117] Wuntakal R, et al. Luteinising hormone releasing hormone (LHRH) agonists for the treatment of relapsed epithelial ovarian cancer. Cochrane Database Syst Rev 2016;29(June (6))CD011322</td></tr>
<tr><td rowspan="2">Leitlinienprogramm Onkologie, 2016 [6,7].<br><br>Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)<br><br>Maligne Ovarialtumore: Diagnostik, Therapie und Nachsorge</td><td>Fragestellung/Zielsetzung<br><br>Fortgeschrittenes Ovarialkarzinom: Welche ist/sind die derzeitigen Standardtherapie(n) (Substanzen, Applikationswege ((intravenös, intraperitoneal incl. HIPEC)), Therapiedauer, etc.)?<br><br>Fortgeschrittenes Ovarialkarzinom: Welche Rolle spielen Dosisdichte und Dosisintensität?<br><br>Fortgeschrittenes Ovarialkarzinom: Profitieren Patientinnen von einer Erhaltungs- bzw. Konsolidierungstherapie (z.B. medikamentös, strahlentherapeutisch, etc.)?<br><br>Fortgeschrittenes Ovarialkarzinom: Gibt es Subgruppen von Patientinnen (z.B. histol. Typ, Grading, Tumorrest etc.), die mehr oder weniger oder gar nicht von einer bestimmten Therapie profitieren?<br><br>Wie werden Rezidivpopulationen definiert, die eine spezifische Therapie benötigen? Wann ist eine Therapie mit welchen therapeutischen Zielen indiziert?<br><br>Welche Standardtherapien in Abhängigkeit der Rezidivpopulation existieren und wie sollen diese durchgeführt werden?</td></tr>
<tr><td>Methodik<br><br>Grundlage der Leitlinie: evidenz- und konsensbasiert (S3), Version 2.0<br><br>Suchzeitraum: Aktualisierungsrecherchen im März 2016<br><br>LoE: nach SIGN
<table>
<tr><th>Grad</th><th>Beschreibung</th></tr>
<tr><td>1++</td><td>Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)</td></tr>
<tr><td>1+</td><td>Gut durchgeführte Metaanalysen, systematische Übersichten von RCTs oder RCTs mit geringem Risiko systematischer Fehler (Bias)</td></tr>
<tr><td>1-</td><td>Metaanalysen, systematische Übersichten von RCTs oder RCTs mit hohem Risiko systematischer Fehler (Bias)</td></tr>
<tr><td>2++</td><td>Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder<br><br>Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist</td></tr>
<tr><td>2+</td><td>Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist</td></tr>
</table></td></tr>
</table>

| | |
|---|---|
| **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 |

Freitext/Empfehlungen/Hinweise

### *8.2. Systemische Primärtherapie des fortgeschrittenes Ovarialkarzinoms*

*Subgruppen*

Die überwiegende Mehrzahl der fortgeschrittenen Ovarialkarzinome sind seröse „high-grade“ Karzinome (zumeist G3). In molekularen Untersuchungen unterscheiden sich diese deutlich von serösen „low-grade“ Karzinomen sowie anderen histologischen Subtypen wie muzinösen, endometrioiden oder klarzelligen Karzinomen. Es gibt Anzeichen dafür, dass das Ansprechen der verschiedenen molekularen und histologischen Subtypen sich hinsichtlich bestimmter Therapien ebenfalls unterscheidet. Muzinöse Ovarialkarzinome beispielsweise sprechen vermeintlich schlechter auf Carboplatin/Paclitaxel an, ebenso scheint das Ansprechen von G1-Tumoren deutlich geringer zu sein als bei G3-Tumoren. Da die bisherigen Erkenntnisse hierzu jedoch nur hypothesengenerierend sind, kann derzeit eine Abweichung vom Therapiestandard für einzelne Subgruppen von Patientinnen nicht empfohlen werden [151, 152, 192, 205, 213, 314-329].

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213. Aletti, G.D., et al., Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. Gynecol Oncol, 2011. 120(1): p. 23-8.

314. Voest, E.E., J.C. van Houwelingen, and J.P. Neijt, A meta-analysis of prognostic factors in advanced ovarian cancer with median survival and overall survival (measured with the log (relative risk)) as main objectives. Eur J Cancer Clin Oncol, 1989. 25(4): p. 711-20.

315. van Houwelingen, J.C., et al., Predictability of the survival of patients with advanced ovarian cancer. J Clin Oncol, 1989. 7(6): p. 769-73.

316. Silvestrini, R., et al., Cell kinetics: a prognostic marker in epithelial ovarian cancer. Gynecol Oncol, 1989. 35(1): p. 15-9.

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318. Lund, B. and P. Williamson, Prognostic factors for overall survival in patients with advanced ovarian carcinoma. Ann Oncol, 1991. 2(4): p. 281-7.

319. Omura, G.A., et al., Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. J Clin Oncol, 1991. 9(7): p. 1138-50.

320. Gadducci, A., et al., Serum half-life of CA 125 during early chemotherapy as an independent prognostic variable for patients with advanced epithelial ovarian cancer: results of a multicentric Italian study. Gynecol Oncol, 1995. 58(1): p. 42-7.

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323. van Dalen, A., et al., Prognostic significance of CA 125 and TPS levels after 3 chemotherapy courses in ovarian cancer patients. Gynecol Oncol, 2000. 79(3): p. 444-50.

324. Camilleri-Broet, S., et al., HER-2 overexpression is an independent marker of poor prognosis of advanced primary ovarian carcinoma: a multicenter study of the GINECO group. Ann Oncol, 2004. 15(1): p. 104-12.

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327. Kommoss, S., et al., Histological grading in a large series of advanced stage ovarian carcinomas by three widely used grading systems: consistent lack of prognostic significance. A translational research subprotocol of a prospective randomized phase III study (AGO-OVAR 3 protocol). Virchows Arch, 2009. 454(3): p. 249-56.

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329. Mackay, H.J., et al., Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. Int J Gynecol Cancer, 2010. 20(6): p. 945-52.

Die einzige Ausnahme hier sind die früher als Borderline-Tumoren mit invasiven Implants kategorisierten Tumoren, die nur aufgrund einer Änderung der WHO-Klassifikation nun als low-grade Karzinome klassifiziert werden. Es gibt keine Daten, die einen möglichen Benefit einer Systemtherapie bei diesem Kollektiv aufzeigen.

## 9. Rezidivtherapie

### *9.1. Rezidivpopulationen*

| **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.<br>Platinresistentes Ovarialkarzinom: Erkrankung zeigt ein Rezidiv innerhalb der ersten 6 Monate nach Abschluss der initialen platinhaltigen Chemotherapie.<br>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 [266]<br>Primärstudien: [52, 330-338] | | |

2. Scottish Intercollegiate Guidelines Network, SIGN #75: Epithelial ovarian cancer. A national clinical guideline. 2003: Scottish Intercollegiate Guidelines Network

266: siehe oben

52. Rustin, G.J., et al., Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet, 2010. 376(9747): p. 1155-63.

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<table>
<tr><td></td><td>
335. Blackledge, G., et al., Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer, 1989. 59(4): p. 650-3.<br><br>
336. Eisenhauer, E.A., et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). 2009(1879-0852 (Electronic)).<br><br>
337. Rustin, G.J., et al., Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer, 2011. 21(2): p. 419-23.<br><br>
338. Friedlander, M., et al., Clinical trials in recurrent ovarian cancer. 2011(1525-1438 (Electronic)).<br><br>
9.2. Systemische Rezidivtherapie<br><br>
9.2.2. Rezidivtherapie basierend auf einer erneuten platinhaltigen Therapie (ehemals platin-sensitives Rezidiv)<br><br>
<table>
<tr><th>8.6.</th><th>Konsensbasierte Empfehlung</th><th>2013</th></tr>
<tr><td>EK</td><td colspan="2">Patientinnen mit platinsensitivem Ovarialkarzinomrezidiv sollen, wenn eine Indikation zur Chemotherapie besteht, eine platinhaltige Kombinationstherapie erhalten. Folgende Kombinationen können in Betracht gezogen werden:<br>• Carboplatin/Gemcitabin/Bevacizumab*<br>• Carboplatin/pegyliertes liposomales Doxorubicin<br>• Carboplatin/Paclitaxel<br>• Carboplatin/Gemcitabin<br><br>*bei Patientinnen mit erstem Rezidiv und ohne vorherige VEGF gerichtete Therapie</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Scottish Intercollegiate Guidelines Network (SIGN), 2013 [15].<br><br>Management of epithelial ovarian cancer</td><td>
Zielsetzung<br><br>
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.
</td></tr>
<tr><td>
Methodik<br><br>
Grundlage der Leitlinie: repräsentative Leitliniengruppe, CoI jährlich dargelegt, Entwicklungsprozess folgt der Systematik der evidenzbasierten Medizin, öffentliche und fachbezogene Konsultation, Finanzierung des Projektes unklar<br><br>
Suchzeitraum: 2003 bis 2012<br><br>
LoE:<br><br>
1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias<br><br>
1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias<br><br>
1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias<br><br>
2++ High quality systematic reviews of case control or cohort studies<br><br>
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal<br><br>
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<br><br>
2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
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| | 3 Non-analytic studies, eg case reports, case series<br><br>4 Expert opinion<br><br>GoR:<br><br>*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.*<br><br>**A** At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*<br><br>A body of evidence consisting principally of studies rated as 1+,<br><br>directly applicable to the target population, and demonstrating overall consistency of results<br><br>**B** A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*<br><br>Extrapolated evidence from studies rated as 1++ or 1+<br><br>**C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*<br><br>Extrapolated evidence from studies rated as 2++<br><br>**D** Evidence level 3 or 4; *or*<br><br>Extrapolated evidence from studies rated as 2+<br><br>GOOD PRACTICE POINTS: Recommended best practice based on the clinical experience of the guideline development group<br><br>Sonstige methodische Hinweise: Suche und Auswahl der Literatur nicht vollständig dargelegt, CoI nur auf Anfrage einsehbar, Ableitung der Empfehlungen und Konsensprozesse unklar |
| | Freitext/Empfehlungen/Hinweise<br><br>**6.3 relapsed disease**<br><br>*6.3.1 systemic therapy in recurrent ovarian cancer*<br><br>157. Jaaback K, et al. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2011, Issue 11.<br><br>158. Fung-Kee-Fung M, et al. Optimal chemotherapy treatment for women with recurrent ovarian cancer. Curr Oncol 2007;14(5):195-208.<br><br>159. Holloway RW, et al. Tolerability, efficacy, and safety of pegylated liposomal Doxorubicin in combination with Carboplatin versus gemcitabine-Carboplatin for the treatment of platinum-sensitive recurrent ovarian cancer: a systematic review. Oncologist 2010;15(10):1073-82.<br><br>160. Main C, et al. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation. Health Technol Assess 2006;10(9):1-132. iii-iv.<br><br>161. Kyrgiou M, et al. Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments. J Natl Cancer Inst 2006;98(22):1655-63.<br><br>162. Aghajanian C, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30(17):2039-45. |

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| | 163. Ferrandina G, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol 2008;26(6):890-6.<br><br>164. Gladieff L, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: Results from a subset analysis of the CALYPSO phase III trial. Ann Oncol 2012;23(5):1185-9.<br><br>165. Joly F, et al. Decreased hypersensitivity reactions with carboplatin pegylated liposomal doxorubicin compared to carboplatin paclitaxel combination: analysis from the GCIG CALYPSO relapsing ovarian cancer trial. Gynecol Oncol 2011;122(2):226-32.<br><br>166. Kurtz JE, et al. Ovarian cancer in elderly patients: Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in late relapse: A gynecologic cancer intergroup (GCIG) CALYPSO substudy. Ann Oncol 2011;22(11):2417-23.<br><br>167. Meier W, et al. Topotecan versus treosulfan, an alkylating agent, in patients with epithelial ovarian cancer and relapse within 12 months following 1st-line platinum/paclitaxel chemotherapy. A prospectively randomized phase III trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGOOVAR). Gynecol Oncol 2009;114(2):199-205.<br><br>168. Monk BJ, et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;28(19):3107-14.<br><br>169. Mutch DG, 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.<br><br>170. Pfisterer J, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: An intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24(29):4699-707.<br><br>171. Poveda A, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6-12 months) subpopulation of OVA-301 phase III randomized trial. Ann Oncol 2011;22(1):39-48.<br><br>172. Pujade-Lauraine E, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010;28(20):3323-9.<br><br>173. Sehouli J, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: A randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2011;29(2):242-8.<br><br>174. Sehouli J, et al. Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. J Clin Oncol 2008;26(19):3176-82.<br><br>175. Wagner U, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. Br J Cancer 2012;107(4):588-91.<br><br>**1+ bis 1++**<br><br>Women with platinum-sensitive relapsed ovarian cancer should be treated with a platinum based combination with paclitaxel, PLDH or gemcitabine. **(GoR: A)**<br><br>*6.3.2 The role of hormonal therapy in relapsed disease*<br><br>176. Argenta PA, et al. A phase II study of fulvestrant in the treatment of multiply recurrent epithelial ovarian cancer. Gynecol Oncol 2009;113(2):205-9. |

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| | 177. Balbi G, et al. Second-line therapy of advanced ovarian cancer with GnRH analogs. Int J Gynecol Cancer 2004;14(5):799-803.<br><br>178. Bowman A, et al. CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: identification of an endocrine-sensitive subgroup. Clin Cancer Res 2002;8(7):2233-9.<br><br>179. Karagol H, et al. The efficacy of tamoxifen in patients with advanced epithelial ovarian cancer. Med Oncol 2007;24(1):39-43.<br><br>180. Papadimitriou CA, et al. Hormonal therapy with letrozole for relapsed epithelial ovarian cancer. Long-term results of a phase II study. Oncology 2004;66(2):112-7.<br><br>181. Ramirez PT, et al. Efficacy of letrozole in the treatment of recurrent platinum- and taxane-resistant high-grade cancer of the ovary or peritoneum. Gynecol Oncol 2008;110(1):56-9.<br><br>182. Smyth JF, et al. Antiestrogen therapy is active in selected ovarian cancer cases: The use of letrozole in estrogen receptor-positive patients. Clin Cancer Res 2007;13(12):3617-22.<br><br>183. V erschraegen CF, et al. Phase II study of cetrorelix, a luteinizing hormone-releasing hormone antagonist in patients with platinum-resistant ovarian cancer. Gynecol Oncol 2003;90(3):552-9.<br><br>184. Williams C, et al. Tamoxifen for relapse of ovarian cancer. Cochrane Database of Systematic Reviews 2010, Issue 3.<br><br>**LoE 3**<br><br>Hormonal therapy with tamoxifen or an aromatase inhibitor can be used for women with recurrent, platinum-resistant, ovarian cancer or in those wishing to avoid or delay further chemotherapy, particularly where their original tumour is expressing the oestrogen receptor. **(GoR: D)** |
| **National Institute for Health and Care Excellence (NICE), 2011 [11,12].**<br><br>Ovarian cancer: recognition and initial management | Fragestellung<br><br>• What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy?<br><br>• For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management? |
| | Methodik<br><br>Grundlage der Leitlinie: multidisziplinäre und repräsentative Leitliniengruppe, CoI dargelegt, finanzielle Unabhängigkeit erklärt, Entwicklungsprozess folgt der Systematik der evidenzbasierten Medizin, informale Konsentierung der Empfehlungen, Stellungnahmeverfahren vor Veröffentlichung<br><br>Suchzeitraum: letzte Überprüfung bis 2016<br><br>LoE/GoR: GRADE-Systematik und Formulierung<br><br>Sonstige methodische Hinweise: „We checked this guideline in March 2016 and we are updating the recommendations on detection in primary care and establishing a diagnosis in secondary care.“ |

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| | Freitext/Empfehlungen/Hinweise<br><br>**1.4 Management of advanced (stage II–IV) ovarian cancer**<br><br>Note that recommendations 1.1 and 1.2 in NICE technology appraisal guidance 55 (Guidance on the use of paclitaxel in the treatment of ovarian cancer) are on first-line chemotherapy in the treatment of ovarian cancer.<br><br>**NICE technology appraisal guidance 55 (Guidance on the use of paclitaxel in the treatment of ovarian cancer) [10]**<br><br>Recommendations 1.3, 1.4 and 1.5 have been updated and replaced by NICE technology appraisal guidance 91 (Anmerkung: "This guidance has been updated and replaced by NICE technology appraisal guidance 389.")<br><br>**NICE technology appraisal guidance 389 (Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer) [13]**<br><br>1.1 Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.<br><br>1.2 Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.<br><br>1.3 PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.[1][2]<br><br>1.4 The following are not recommended within their marketing authorisations for treating the first recurrence of platinum-sensitive ovarian cancer:<br><br>• gemcitabine in combination with carboplatin<br>• trabectedin in combination with PLDH<br>• topotecan.<br><br>The appraisal committee was unable to make recommendations on the use of these technologies for treating platinum-sensitive ovarian cancer beyond the first recurrence.<br><br>1.6 People whose treatment with gemcitabine in combination with carboplatin, trabectedin in combination with PLDH, or topotecan is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.<br><br>[1] At the time of publication (April 2016), PLDH (Caelyx) in combination with platinum did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility |

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| | for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.<br><br>[2] The use of PLDH (Caelyx) in combination with platinum is outside the terms of the marketing authorisation for Caelyx. Consequently the statutory funding requirement does not apply to this recommendation. NICE received a remit to appraise this combination under Regulation 5 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013.<br><br>Availability, nature and quality of evidence:<br><br>The committee expressed disappointment with the quality and breadth of the trial evidence, and also with some of the trial design and reporting, but on balance concluded that the assessment group's approach was reasonable given the data available, and accepted the clinical-effectiveness results from the network meta-analyses.<br><br>Uncertainties generated by the evidence<br><br>The committee discussed the limitations of the network meta-analyses, particularly the differences in baseline characteristics between trials, uncertainty around whether trials were adequately powered to detect differences in overall survival and progression-free survival, and concerns about confounding because of crossover. The committee acknowledged that the analyses had methodological limitations and that some assumptions had to be accepted. |

**Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren**

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| **National Institute for Health and Care Excellence (NICE), 2013 [9].**<br><br>Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer, TA285 | 1.1 Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.<br><br>1.2 People currently receiving bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer should be able to continue treatment until they and their clinician consider it appropriate to stop.<br><br><u>Availability, nature and quality of evidence</u><br><br>The key evidence for the clinical effectiveness of bevacizumab plus gemcitabine and carboplatin came from 1 randomised controlled trial (OCEANS). This double-blind, randomised, placebo-controlled trial assessed the safety and efficacy of bevacizumab plus gemcitabine and carboplatin in 484 adults with platinum-sensitive recurrent epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer, with a first recurrence of ovarian cancer and who had not previously received VEGF receptor-targeted agents.<br><br><u>Uncertainties generated by the evidence</u><br><br>The Committee concluded that, although the trial showed an increase in PFS for bevacizumab plus gemcitabine and carboplatin compared with gemcitabine and carboplatin, it was unclear what effect censoring might have had on these results.<br><br>The Committee concluded that no overall survival benefit for bevacizumab plus gemcitabine and carboplatin had been shown in the OCEANS trial, but the results could have been confounded by post-progression therapies.<br><br>The Committee concluded that there were various theoretical explanations for the mismatch between the PFS and overall survival results, but was unable to draw any firm conclusions on which of these explained the mismatch, and to what extent.<br><br><u>Estimate of the size of the clinical effectiveness including strength of supporting evidence</u><br><br>The Committee noted that the results for the intention-to-treat population at the September 2010 cut-off date gave a difference in median PFS of 4 months in favour of bevacizumab and this was statistically significant. |

**Detaillierte Darstellung der Recherchestrategie**

**Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 26.06.2017**

| # | 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 |
| 5 | (fallopian next tube*):ti,ab,kw or tubal:ti,ab,kw |
| 6 | (primary next peritoneal):ti,ab,kw or (serous next surface next papillary):ti,ab,kw |
| 7 | #4 or #5 or #6 |
| 8 | #7 and (tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or cancer*):ti,ab,kw |
| 10 | #1 or #2 or #3 or #8 |
| 11 | #10 Publication Year from 2012 to 2017 |

**SR, HTAs in Medline (PubMed) am 27.06.2017**

| # | Suchfrage |
|---|---|
| 4 | ((((ovarian neoplasms/) OR Fallopian Tube Neoplasms/) OR Peritoneal Neoplasms/)) OR "Ovarian epithelial cancer" [Supplementary Concept] |
| 5 | ((((((ovar*[Title/Abstract) OR "fallopian tube"[Title/Abstract]) OR tubal[Title/Abstract]) OR oviduct[Title/Abstract]) OR "primary peritoneal"[Title/Abstract]) OR "serous surface papillary"[Title/Abstract]) OR peritoneum[Title/Abstract] |
| 6 | (#5) AND (((((((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour[Title/Abstract]) OR tumour[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]) |
| 7 | #4 OR #6 |
| 8 | (#7) 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])))) |
| 9 | ((#8) AND ("2012/06/01"[PDAT] : "2017/06/30"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) |
| 10 | (#9) 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 |

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|---|---|
| | pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]) |

**Leitlinien in Medline (PubMed) am 27.06.2017**

| # | **Suchfrage** |
|---|---|
| 1 | ((("Ovarian Neoplasms"[MeSH]) OR "Ovarian epithelial cancer"[Supplementary Concept]) OR Fallopian Tube Neoplasms[MeSH]) OR Peritoneal Neoplasms[MeSH] |
| 2 | (((((ovar*[Title/Abstract) OR “fallopian tube”[Title/Abstract]) OR tubal[Title/Abstract]) OR oviduct[Title/Abstract]) OR “primary peritoneal”[Title/Abstract]) OR “serous surface papillary[Title/Abstract] |
| 3 | (#2) AND (((((((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour[Title/Abstract]) OR tumour[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]) |
| 4 | (#1) OR #3 |
| 5 | (#4) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp]))) |
| 6 | ((#5) AND ("2012/06/01"[PDAT] : "2017/06/30"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal])) |

**Anhang:**

**Table 2: Efficacy results of 5 RCTs**

| References | Arms | Sample Size | Patient Characteristic | Primary Endpoint | PFS | | | OS | | | ORR (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Median (months) | HR | HR, 95% CI | Median (months) | HR | HR, 95% CI | |
| GOG218 | TC+PL | 625 | Newly diagnosed | PFS | 10.3 | 0.770 | 0.681-0.870 | 39.3 | 0.885 | 0.750-1.040 | NR |
| | TC+Bev+Bev(m) | 623 | | | 14.1 | | | 39.7 | | | NR |
| ICON7 | TC | 764 | Newly diagnosed | PFS | 17.5 | 0.930 | 0.830-1.050 | 58.6 | 0.990 | 0.850-1.140 | 48.0 |
| | TC+Bev+Bev(m) | 764 | | | 19.9 | | | 58.0 | | | 67.0 |
| OCEANS | GC+PL | 242 | Recurrent | PFS | 8.4 | 0.484 | 0.388-0.605 | 32.9 | 0.952 | 0.771-1.176 | 57.4 |
| | GC+Bev+Bev(m) | 242 | | | 12.4 | | | 33.6 | | | 78.5 |
| AURELIA | CT(PLD or PAC or TOP) | 182 | Recurrent | PFS | 3.4 | 0.480 | 0.380-0.600 | 13.3 | 0.850 | 0.660-1.080 | 12.6 |
| | CT+Bev+Bev(m) | 179 | | | 6.7 | | | 16.6 | | | 30.9 |
| GOG213 | TC | 374 | Recurrent | OS | 10.4 | 0.614 | 0.522-0.722 | 37.3 | 0.827 | 0.683-1.005 | NR |
| | TC+Bev+Bev(m) | 374 | | | 13.8 | | | 42.2 | | | NR |

TC, Paclitaxel+Carboplatin; GC, Gemcitabine+Carboplatin; PL, placebo; Bev(m), Bevacizumab (maintenance chemotherapy); CT, PLD or PAC or TOP; PLD, pegylated liposomal doxorubicin; PAC, weekly paclitaxel; TOP, topotecan; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; CI, confidence interval; NR, not reported.

**Abbildung 8: aus Wu YS et al., 2017 [17]**

**Table 1.** Trial characteristics

| Trial | ICON & AGO | Pfisterer et al. | Alberts et al. | González-Martín et al. | Bolis et al. |
|---|---|---|---|---|---|
| Accrual period (years) | 1996–2002 | 1999–2002 | 2002–2004 | 2000–2002 | 1991–1998 |
| Location | Europe[a] | Europe and Canada | USA | Spain | Italy |
| Patients randomized | 802 | 356 | 61 | 81 | 190 |
| FIGO stage | Not available | I–IV | III–IV | I–IV | II–IV |
| Median follow-up (months) | 42.5 | 27.1 | 59.3 | 13.7 | Not available |
| Planned carboplatin dose | AUC 5 Cisplatin: 50 mg/m$^2$ (75 mg/m$^2$ in controls) | AUC 4 (AUC 5 in controls) | AUC 5 | AUC 5 | 300 mg/m$^2$ |
| Planned combination dose | Paclitaxel: 175 mg/m$^2$ ICON 185 mg/m$^2$ AGO | Gemcitabine 1000 mg/m$^2$ d1,d8 q3 weeks. | PLD[b] 30 mg/m$^2$ | Paclitaxel 175 mg/m$^2$ | Epidoxorubicin 120 mg/m$^2$ |
| Planned treatment duration | MRC CTU: ≥6 cycles Italy: 3–6 cycles AGO: 6–8 cycles every 3 weeks | 6–10 cycles every 3 weeks | Every 4 weeks | 6–9 cycles every 3 weeks | 5 cycles every 4 weeks |

[a]UK, Norway and Switzerland; Germany; Italy.
[b]Pegylated liposomal doxorubicin.
FIGO, international federation of gynecology and obstetrics; MRC CTU: medical research council clinical trials unit

**Abbildung 9: aus Raja FA et al., 2013 [14]**

TABLE 8 Summary of studies included in the review of the clinical effectiveness literature

| Study and principal citation | Trial design | Population (*n*) | PFI | Randomised treatments | | Supplementary publications |
|---|---|---|---|---|---|---|
| | | | | Intervention | Comparator | |
| ***Both intervention and comparator used within licensed indication and at licensed dose*** | | | | | | |
| ten Bokkel Huinink *et al.*[21] | Phase III, multicentre, open-label RCT | 235 | Disease that recurred or progressed after first-line platinum based therapy (no minimum PFI specified) | Topotecan (1.5 mg/m² as a 30-minute i.v. infusion) for five consecutive days every 21 days | Paclitaxel (175 mg/m² as a 3-hour i.v. infusion) every 21 days | ten Bokkel Huinink *et al.*[52]<br>Gore *et al.*[53] |
| Gordon *et al.*[49] | Phase III, multicentre, open-label RCT | 474 | Disease that recurred after, or failed, first-line platinum-based chemotherapy (no minimum PFI specified) | PLDH (50 mg/m² as a 1-hour i.v. infusion) every 28 days | Topotecan (1.5 mg/m² as a 30-minute infusion) for five consecutive days every 21 days | Gordon *et al.*[54] |
| Trial 30–57; data taken from TA91[13] | Phase III, multicentre, open-label RCT | 216 | Disease that recurred after, or failed, one platinum-based first-line regimen (no minimum PFI specified) | PLDH (50 mg/m²) every 28 days | Paclitaxel (175 mg/m²) every 21 days | One conference abstract (O'Byrne *et al.*[47]) |
| Gonzalez-Martin *et al.*[48] | Phase II, 'pick the winner' design, multicentre RCT; level of masking unclear | 81 | Progression > 6 months after completion of platinum-based chemotherapy | Paclitaxel (175 mg/m² as a 3-hour i.v. infusion) plus carboplatin (AUC 5) every 3 weeks | Carboplatin alone (AUC 5) every 3 weeks | None identified |
| Pfisterer *et al.*[50] | Phase III, multicentre, international, open-label RCT | 356 | Disease recurrence at least 6 months after completion of first-line, platinum-based therapy | Gemcitabine (1000 mg/m²) plus carboplatin (AUC 4) every 21 days | Carboplatin alone (AUC 5) every 21 days | None identified |

**Abbildung 10: aus Edwards SJ et al., 2015 [2]**

**TABLE 11** Overall survival for patients with platinum-sensitive ovarian cancer

| Trial name | Intervention | Comparator | HR (95% CI) |
|---|---|---|---|
| CALYPSO (Pujade-Lauraine *et al.*[56]) | PLDH (30 mg/m²) plus carboplatin every 21 days | Paclitaxel (175 mg/m²) plus carboplatin every 21 days | 0.99[a] (0.85 to 1.16) |
| Bafaloukos *et al.*[29] | PLDH (45 mg/m²) plus carboplatin every 28 days | Paclitaxel (175 mg/m²) plus carboplatin every 21 days | 1.15 (0.78 to 1.66) |
| ICON4/AGO-OVAR 2.2 (Parmar *et al.*[61]) | Paclitaxel plus platinum | Conventional platinum treatment | 0.82 (0.69 to 0.97) |
| Gonzalez-Martin *et al.*[48] | Paclitaxel (175 mg/m²) plus carboplatin every 21 days | Carboplatin alone every 21 days | 0.31 (0.14 to 0.68) |
| ten Bokkel Huinink *et al.*[52] | Topotecan (1.5 mg/m²) for 5 days every 21 days | Paclitaxel (175 mg/m²) every 21 days | 1.01 (0.66 to 1.54) |
| Trial 30–57 (taken from TA91)[13] | PLDH (50 mg/m²) every 28 days | Paclitaxel (175 mg/m²) every 21 days | 1.05 (0.66 to 1.66) |
| Gordon *et al.*[54] | PLDH (50 mg/m²) every 28 days | Topotecan (1.5 mg/m²) for 5 days every 21 days | 1.43[b] (1.06 to 1.92) |
| Alberts *et al.*[28] | PLDH (30 mg/m²) plus carboplatin every 4 weeks | Carboplatin alone every 4 weeks | 0.70 (0.40 to 1.21) |
| OVA-301 (Monk *et al.*[30]) | Trabectedin (1.1 mg/m²) plus PLDH (30 mg/m²) every 3 weeks | PLDH (50 mg/m²) every 4 weeks | 0.83 (0.67 to 1.04) |
| Pfisterer *et al.*[50] | Gemcitabine (1000 mg/m²) plus carboplatin every 21 days | Carboplatin alone every 21 days | 0.96 (0.75 to 1.23) |

a HR as reported is for paclitaxel plus carboplatin vs. PLDH plus carboplatin, i.e. HR of < 1 favours paclitaxel plus carboplatin.
b HR of > 1 favours PLDH.

**Abbildung 11: aus Edwards SJ et al., 2015 [2]**

**TABLE 14** Overall survival for the subgroup of patients with FPS ovarian cancer

| Trial | Intervention | Comparator | HR (95% CI) |
|---|---|---|---|
| CALYPSO[56] | PLDH (30 mg/m²) plus carboplatin every 21 days | Paclitaxel (175 mg/m²) plus carboplatin every 3 weeks | 0.99 (0.81 to 1.21) |
| ICON4/AGO-OVAR 2.2[61] | Paclitaxel plus platinum | Conventional platinum treatment | NR |
| Gordon *et al.*[54] | PLDH (50 mg/m²) every 28 days | Topotecan (1.5 mg/m²) daily for 5 days every 21 days | 1.15[a] (0.714 to 1.852) |
| OVA-301[30,64] | Trabectedin (1.1 mg/m²) plus PLDH (30 mg/m²) every 21 days | PLDH (50 mg/m²) every 4 weeks | 0.89[b] (0.58 to 1.35) |

NR, not reported.
a HR of > 1 favours PLDH.
b HR taken from TA222.[15]

**Abbildung 12: aus Edwards SJ et al., 2015 [2]**

**TABLE 15** Overall survival for the subgroup of patients with PPS ovarian cancer

| Trial | Intervention | Comparator | HR (95% CI) |
|---|---|---|---|
| CALYPSO[56] | PLDH (30 mg/m²) plus carboplatin every 21 days | Paclitaxel (175 mg/m²) plus carboplatin every 3 weeks | 1.01 (0.80 to 1.28) |
| ICON4/AGO-OVAR 2.2[61] | Paclitaxel plus platinum | Conventional platinum treatment | NR |
| Gordon *et al.*[54] | PLDH (50 mg/m²) every 28 days | Topotecan (1.5 mg/m²) daily for 5 days every 21 days | 1.58[a] (1.07 to 2.33) |
| OVA-301[30,64] | Trabectedin (1.1 mg/m²) plus PLDH (30 mg/m²) every 21 days | PLDH (50 mg/m²) every 4 weeks | 0.64 (0.47 to 0.86) |

NR, not reported.
a HR of > 1 favours PLDH.

**Abbildung 13: aus Edwards SJ et al., 2015 [2]**

**TABLE 17** Overall survival for the subgroup of patients with PRR ovarian cancer

| Trial name | Intervention | Comparator | HR (95% CI) |
|---|---|---|---|
| ten Bokkel Huinink *et al.*[52] | Topotecan (1.5 mg/m²) for 5 days every 21 days | Paclitaxel (175 mg/m²) every 21 days | 0.74 (0.5 to 1.09) |
| Trial 30–57 (taken from TA91[13]) | PLDH (50 mg/m²) every 28 days | Paclitaxel (175 mg/m²) every 21 days | 0.87 (0.61 to 1.24) |
| Gordon *et al.*[54] | PLDH (50 mg/m²) every 28 days | Topotecan (1.5 mg/m²) for 5 days every 21 days | 1.07[a] (0.82 to 1.39) |
| Sehouli *et al.*[23] | Topotecan (4.0 mg/m²) (weekly; days 1, 8 and 15) every 28 days | Topotecan (1.25 mg/m²) for five consecutive days every 21 days | 1.04 (0.74 to 1.44) |
| Lortholary *et al.*[62] | Weekly paclitaxel (80 mg/m²) plus carboplatin | Weekly paclitaxel (80 mg/m²) on 4-week cycle | 1.07 (0.86 to 1.34) |

a HR of > 1 favours PLDH.

**Abbildung 14: aus Edwards SJ et al., 2015 [2]**

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