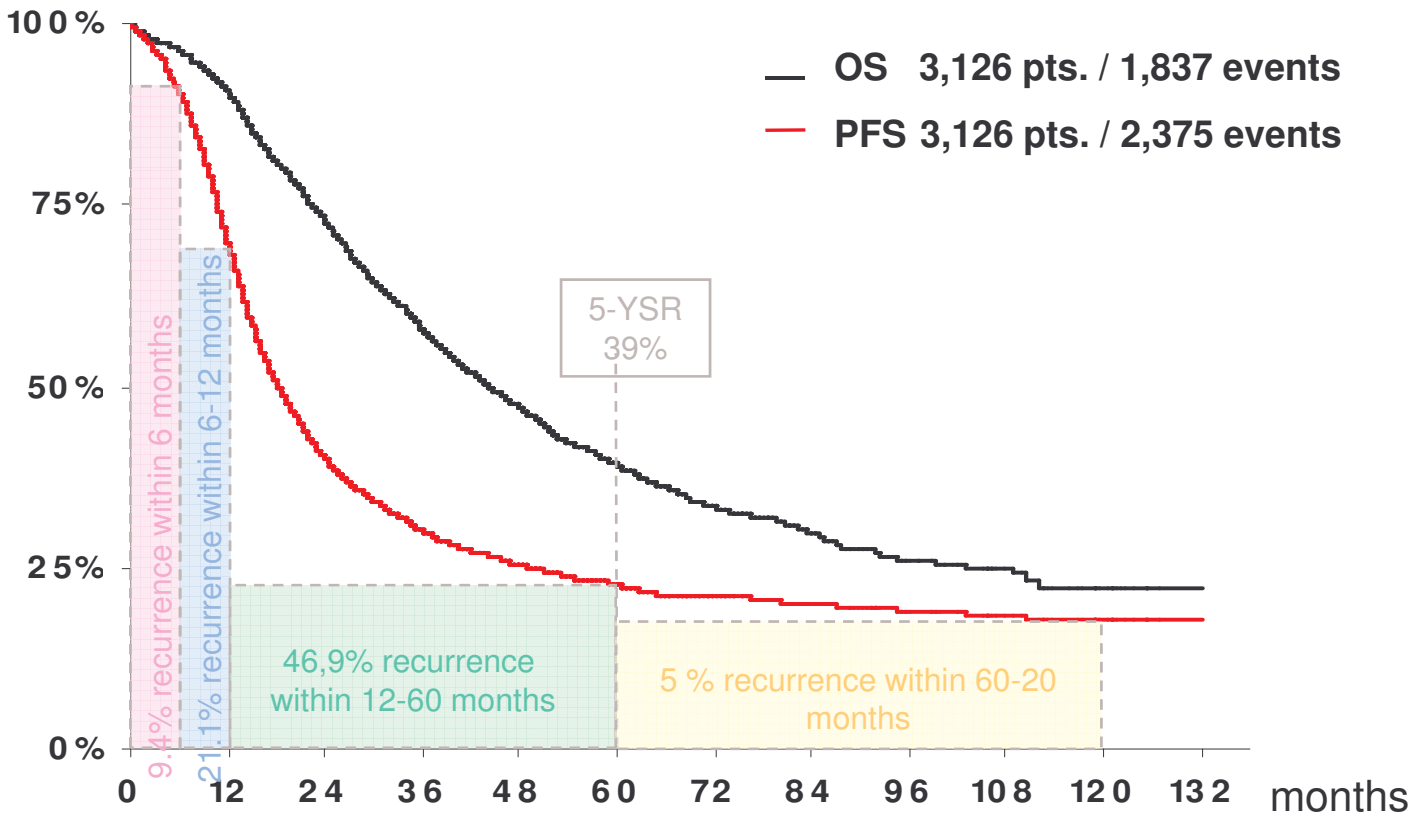
# Leitlinien, Ausblick und aktuelle Studien

## State of the Art

## 2009

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

Overall and progression-free survival in advanced ovarian cancer FIGO IIB-IV (all pts.)
An individual patients metaanalysis of AGO-OVAR 3, AGO-OVAR 5, and AGO-OVAR 7




*du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J: The role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer. A combined exploratory analysis of three prospectively randomized phase III multicenter trials by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux pour les Etudes des Cancers de l'Ovaire (GINECO).*
*Cancer 2009; 15: 1234-1244*

# Kombinationstherapie Platin-Paclitaxel

- Kombinationstherapie (Carboplatin-Paclitaxel) seit Sommer 2003 Standard bei Patientinnen mit platinsensiblem Ovarialkarzinomrezidiv
- Bei 20% der Patientinnen (noch) persistierende Neurotoxizität aus der First-line Therapie
  (-> Selektion !?)
- AGO Teil dieser Studie früher als geplant geschlossen
- In Ovar 2.2 – ICON 4 bei 20% aller Pat. mit Kombination Neurotoxizität ≥ 2. Grades vorhanden (vs. 1% bei Platin-Monotherapie)

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

## GCIG Studie Gem/Carbo vs. Carbo
## AGO-OVAR – NCIC CTG – EORTC GCG
## Design

- Ovarialkarzinomrezidiv > 6 Monate nach Primärtherapieende
- mindestens evaluierbare Erkrankung
- Strata:
  - Therapiefreies Intervall (6-12, > 12 Monate)
  - First-Line Therapie (Plat. +/- Paclitaxel)
  - messbare vs. evaluierbare Erkrankung

RANDOMISIERUNG

Gemcitabin 1000 mg/m² d 1+8
Carboplatin AUC 4 d 1
q 21 x 6 (-10)

Carboplatin AUC 5 d 1
q 21 x 6 (-10)

Pfisterer J et al.: J Clin Oncol 2006; 24: 4699 - 4707

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

## GCIG Studie Gem/Carbo vs. Carbo
## AGO-OVAR – NCIC CTG – EORTC GCG
## Ansprechen (%)

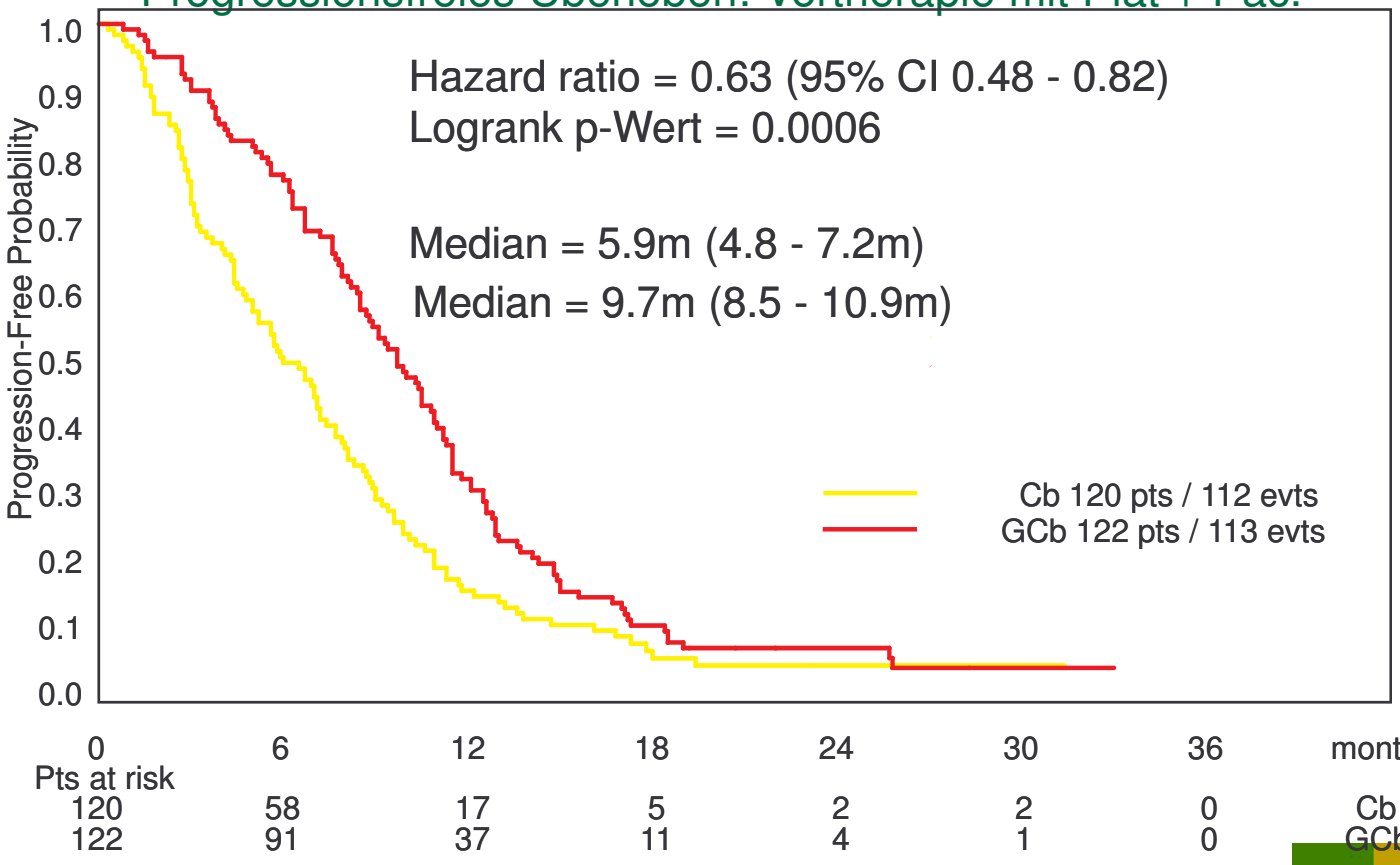
| | Gem/Carbo 178 Pat. | Carbo 178 Pat. |
|---|---|---|
| Nicht beurteilbar | 6.7 | 14.0 |
| Ansprechen | | |
| CR | 14.6 | 6.2 |
| PR | 32.6 | 24.7 |
| SD | 38.2 | 38.8 |
| PD | 7.9 | 16.3 |
| Ansprechen insgesamt | | |
| CR + PR | 47.2 | 30.9 |

p=0.0016

Pfisterer J et al.: J Clin Oncol 2006; 24: 4699 - 4707

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

## GCIG Studie Gem/Carbo vs. Carbo
## AGO-OVAR – NCIC CTG – EORTC GCG
## Progressionsfreies Überleben: Vortherapie mit Plat + Pac.




Pfisterer J et al.: J Clin Oncol 2006; 24: 4699 - 4707

FORSCHEN
LEHREN
HEILEN

# Behandlung des Rezidivs

## Systemische Therapie des platinsensiblen Rezidivs
## Empfehlungen SoA 2007

- **Platinsensibles Rezidiv (> 6 Monate)**

**Die platinhaltige Kombinationstherapie ist der Platinmonotherapie überlegen** **LoE I GoR A**

**Carboplatin / Paclitaxel ist effektiv** **LoE I GoR A**

**Carboplatin / Gemcitabin ist effektiv** **LoE I GoR A**

**Bei Kontraindikation gegen Kombinationstherapie ist bei einem rezidivfreien Intervall von 6-12 Monaten pegyliertes liposomales Doxorubicin effektiv** **LoE II GoR B**

# Rezidivtherapie
# Platinsensibles Rezidiv



Neue Ergebnisse

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200)

Alberts DS et al.: Gynecol Oncol 2008 Jan; 108(1): 90-4.

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200)

| | Carboplatin + PLD<br>31 pat. | Carboplatin<br>30 pat. |
|---|---|---|
| Response rate | 67% | 32% |
| Estimated median PFS | 12 months | 8 months |
| Estimated median OS | 26 months | 18 months |

Conclusion: These data suggest that there may be an advantage to the PLD plus carboplatin combination treatment in patients with PS recurrent OC. The regimen should be further tested.

Alberts DS et al.: Gynecol Oncol 2008 Jan; 108(1): 90-4.

# CALYPSO/AGO-OVAR 2.9

A multinational randomized Phase III
GCIC Intergroup Study
comparing
Pegylated Liposomal Doxorubicin and
Carboplatin (CaC)
versus
Paclitaxel and Carboplatin (TC)
in patients with epithelial ovarian cancer in late relapse
(> 6 months)

EUDRACT # 2004-004456-39
Original Protocol: 01 Nov 2004
Amendment No 1: 03 Mar 2005
Amendment No 2: 04 Jul 2005

# CALYPSO/AGO-OVAR 2.9

**Ovarian cancer in late relapse (> 6 months) after 1st- or 2nd-line platinum-based therapy (previous taxane required)**

**Stratification:**

- **Therapy-free interval (6-12 mo vs > 12 mo)**
- **Measurable disease (yes vs no)**
- **Center**

**R A N D O M I Z E**

**Experimental arm: CD**

**PLD 30 mg/m² IV d 1**

**Carboplatin AUC 5 d 1**

**Q 28 days x 6 courses***

**Control arm: CP**

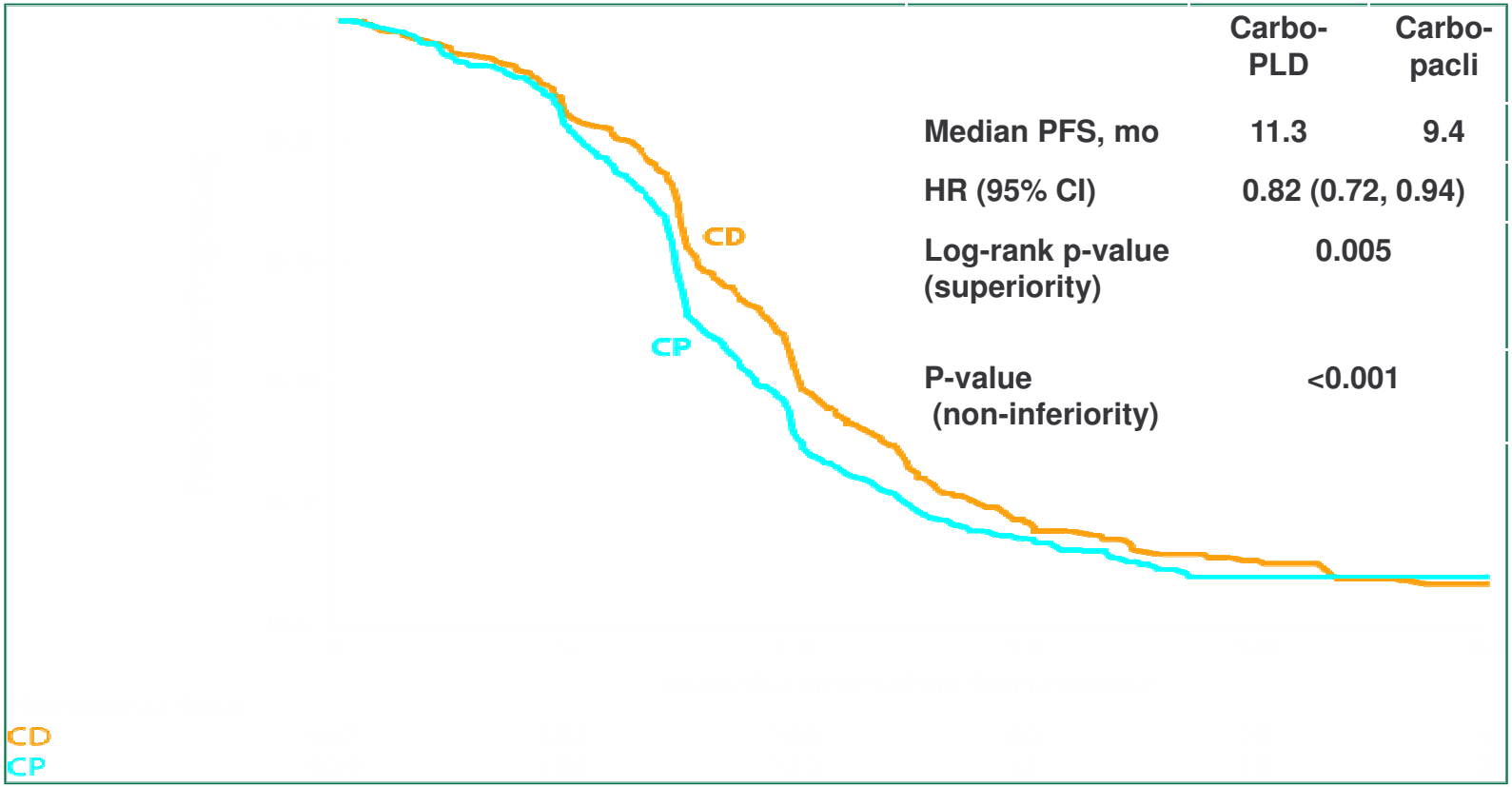
**Paclitaxel 175 mg/m² IV d 1**

**Carboplatin AUC 5 d 1**

**Q 21 days x 6 courses***

*or progression in patients with SD or PR

# CALYPSO/AGO-OVAR 2.9: PFS (ITT)




| | Carbo-PLD | Carbo-pacli |
|---|---|---|
| Median PFS, mo | 11.3 | 9.4 |
| HR (95% CI) | 0.82 (0.72, 0.94) | |
| Log-rank p-value (superiority) | 0.005 | |
| P-value (non-inferiority) | <0.001 | |

# CALYPSO/AGO-OVAR 2.9
# ZUSAMMENFASSUNG

- In patients with platinum-sensitive relapsing ovarian cancer, the combination of PLD-carboplatin was not inferior in term of PFS to paclitaxel-carboplatin, and even was found significantly superior.
  - 18% reduction in risk of recurrence (HR 0.82; P=0.005)
- Survival data immature, with only 322 deaths to date
- Paclitaxel-carboplatin associated with more severe toxicity (carboplatin hypersentivity), alopecia and long-lasting toxicity (neuropathy).
- Moderate HFS, mucositis, nausea/vomiting more frequent with PLD

# CALYPSO/AGO-OVAR 2.9
# SCHLUSSFOLGERUNG

- PLD-carboplatin demonstrated a superior therapeutic index (benefit/risk ratio) versus the current standard, paclitaxel-carboplatin.

- PLD-carboplatin offers an evidence based option in patients with platinum-sensitive ovarian cancer

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

A Randomized Phase III Study of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) *vs* PLD in Relapsed, Recurrent Ovarian Cancer
OVA-301

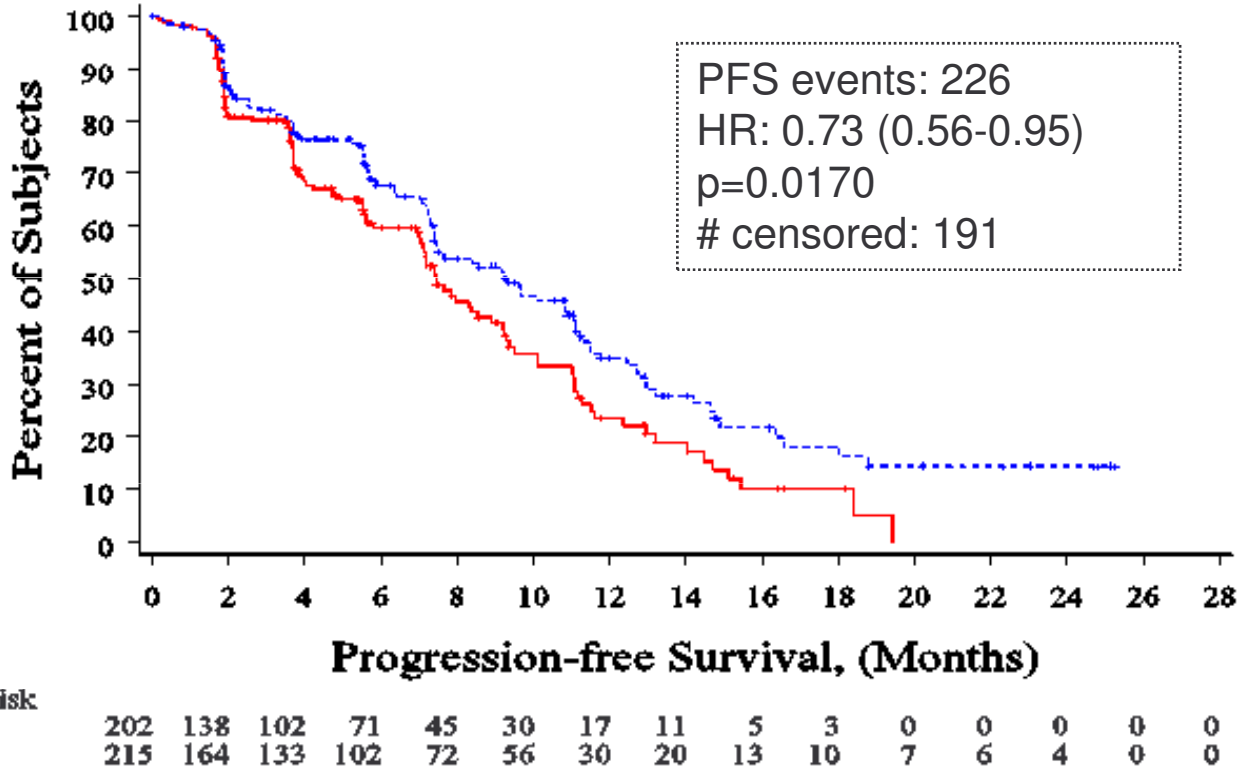
Monk BJ et al.: 12th Biennial Meeting, International Gynecologic Cancer Society, 2008

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

## A Randomized Phase III Study of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) *vs* PLD in Relapsed, Recurrent Ovarian Cancer

OVA-301

Primary End Pont Progression free Survival – PFI>6 Months

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# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

## A Randomized Phase III Study of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) *vs* PLD in Relapsed, Recurrent Ovarian Cancer
## OVA-301
## Best Overall Response (by platinumsensitivity)

| | PLD N=335* | Trabectedin+PLD N=337* | p-value |
|---|---|---|---|
| **Platinum Resistant** | **ORR**** | **ORR**** | |
| Independent Radiology | 12.2% | 13.4% | 0.85 |
| Investigator | 16.3% | 22.7% | 0.26 |
| **Platinum Sensitive** | | | |
| Independent Radiology | 22.6% | 35.3% | 0.0042 |
| Investigator | 32.5% | 47.2% | 0.0022 |

*All randomized subjects
**ORR= Overall response rate

Monk BJ et al.: 12th Biennial Meeting, International Gynecologic Cancer Society, 2008

# REZIDIVTHERAPIE
# PLATINSENSIBLES REZDIV

A Randomized Phase III Study of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) *vs* PLD in Relapsed, Recurrent Ovarian Cancer
OVA-301
Summary

Efficacy:

PFS longer with Trabectedin + PLD by independent radiology review (21% risk reduction)

Higher response rate with the combination (28% vs 19%)

Overall survival data not mature (55% censored)

Safety:

Hand foot syndrome and stomatitis lower with the combination
Cardiac disorders uncommon in both arms
Grades 3 or 4 ANC higher with the combination (72%)
Grades 3 or 4 ALT elevations higher with the combination

Monk BJ et al.: 12th Biennial Meeting, International Gynecologic Cancer Society, 2008

# REZIDIVTHERAPIE
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Laufende Studienprojekte

HECTOR / AGO-OVAR 2.12:
Carboplatin/Topotecan vs. Carboplatin/Paclitaxel oder
Carboplatin/Gemcitabine (oder Carboplatin/PLD)

Neue Studienprojekte

AGO-OVAR 2.14:
Carboplatin/Paclitaxel + ZD4054 vs. Carboplatin/Paclitaxel

MITO 8
Carboplatin/Paclitaxel vs. Caelyx, Cross-Over bei Progreß
Bei Rezidiv 6 – 12 Monate nach primärer platinhaltiger Therapie

# Behandlung des Rezidivs

## Systemische Therapie des platinsensiblen Rezidivs

- **Platin sensibles Rezidiv (> 6 Monate)**

  **Die platinhaltige Kombinationstherapie ist der Platinmonotherapie überlegen.**

  **Carboplatin / Paclitaxel ist effektiv.**

  **Carboplatin / Gemcitabin ist effektiv.**

  **Carboplatin / Peg.lip.Doxorubicin ist effektiv.**

  **Die geeignete Platinkombination sollte auch unter Berücksichtigung des Nebenwirkungsprofils gewählt werden.**

  **Bei Kontraindikation gegen platinhaltige Therapien ist bei einem rezidivfreien Intervall von 6-12 Monaten pegyliertes liposomales Doxorubicin ggf. in Kombination mit Trabectidin effektiv.**