

Internistische Aspekte des Ovarialkarzinoms

OA Dr. Clemens Leitgeb, MBA

Internistische Therapie des Ovarialkarzinoms

- ▶ **Frühstadium** – wo ist Chemotherapie indiziert?
- ▶ Fortgeschrittenes Stadium
 - i.v.-Chemotherapie
 - ▶ First-line
 - Intraperitoneale Chemotherapie
 - Second- und Third-Line
 - Hormontherapie
 - Strahlentherapie
 - Neue Therapien

Standardbehandlung

Stage at Dx	Grade	Surgery	Comb. Chemo.*
1 (limited to ovaries)	1,2	Yes	
1	3,4	Yes	Yes
2 (pelvic extension) 3 (extra-pelvic peritoneal mets)	Any	Yes**	Yes
4 (other distant mets)	Any		Yes

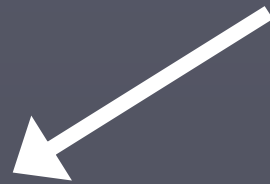
*Standard of care is a Platinum Alkylating Agent Plus a Taxane

** Minimum surgery for stage 2 or 3 is bilateral salpingo-oophorectomy with hysterectomy

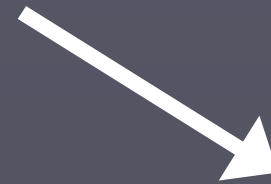
Therapie des Ovarialkarzinoms im Frühstadium Stadium IA-IIA

1. Operation

2. Adjuvante Chemotherapie?



IA-IB, G1: Niedrigrisiko-Tumoren
(5-JÜL 90-100%)



IC-IIA, G3: Hochrisiko-Tumoren
(Rezidivrate: 30%)

'ICON-1' und 'ACTION'

Frühstadien IA - IIA

► 5,5 Jahre F/U, n=975

	Progressionsfreies Überleben	Overall Survival
Chemotherapie	76%	82%
Keine Therapie	65%	74%
	P=.001	P=.008

'ICON-1' und 'ACTION'

- ✓ Geringere Rezidivhäufigkeit durch adjuvante Chemotherapie bei Hochrisiko-Frühkarzinomen
- ✓ Überlebensvorteil bei Hochrisiko-Frühkarzinomen durch adjuvante Chemotherapie
- ✓ Nur wenige Patientinnen ohne adjuvante Therapie
(IA, G1)

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First Line Chemotherapie

Trial	Treatment Regimens	No. of Patients	% Early Crossover	Progression-free Survival (mo)	Overall Survival (mo)
(GOG-132)	Paclitaxel (135 mg/m ² , 24 h) and cisplatin (75 mg/m ²)	201	22%	14.2	26.6
	Cisplatin (100 mg/m ²)	200	40%	16.4*	30.2
	Paclitaxel (200 mg/m ² , 24 h)	213	23%	11.2	26
MRC-ICON3	Paclitaxel (175 mg/m ² , 3 h) and carboplatin AUC 6	478	23%	17.3	36.1
	Carboplatin AUC 6	943	25%	16.1	35.4
	Paclitaxel (175 mg/m ² , 3 h) and carboplatin AUC 6	232	23%	17	40
	Cyclophosphamide (750 mg/m ²) and doxorubicin (75 mg/m ²) and cisplatin (75 mg/m ²)	421	20%	17	40
GOG-111[19]	Paclitaxel (135 mg/m ² , 24 h) and cisplatin (75 mg/m ²)	184	None	18*	38*
	Cyclophosphamide (750 mg/m ²) and cisplatin (75 mg/m ²)	202	None	13	24
OV-10[20]	Paclitaxel (175 mg/m ² , 3 h) and cisplatin (75 mg/m ²)	162	None	15.5*	35.6*
	Cyclophosphamide (750 mg/m ²) and cisplatin (75 mg/m ²)	161	4%	11.5	25.8

'GOG111' und 'OV10'

✓ **Platin + Taxan** ist Standard als First-Line Chemotherapie beim fortgeschrittenen Ovarialkarzinom

? Cisplatin vs. Carboplatin

? Paclitaxel (Taxol) vs. Docetaxel (Taxotere)

Carboplatin vs Cisplatin

- ▶ In 3 Studien verglichen: Cis/Paclitaxel vs Carbo/Paclit.
 - Gleiche Effektivität
 - Geringere Toxizität im Carboplatin-Arm
 - Insbes. sign. geringere Neurotoxizität mit Carboplatin

Greimel et al. JCO 24:579-586,2006

➔ **Carboplatin/Paclitaxel = Standard**

als First-Line Therapie des fortgeschrittenen Ovarialkarzinoms

Carboplatin AUC 5
Paclitaxel 175 mg/m² } X 6 Zyklen

Paclitaxel vs Docetaxel

► SCOTROC-Studie (Vasey, J Natl Cancer Inst, 2004, Nov 17)

	Carbo/ Pac AUC 5 / 175/m2	Carbo/ Doc AUC 5 / 75/m2
Ansprechrate	62%	65%
PFS	14,8 Mo.	15,0 Mo.
OS	68,9 %	64,5 %
Neurotoxizität	30%	11%
G3/4-Neutropenie	84%	94%

 Docetaxel mögliche Alternative zu Paclitaxel

First Line Chemotherapie

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Erweiterte Schemata/Sequenzen

- ▶ 2 Meta-Analysen: **sign. Vorteil** für Hinzunahme eines Anthrazyklins
- ▶ 4 Studien: Cis/Cyclo (CP) vs Cis/Cyclo/Anthrazyklin (CAP)
kein Vorteil
- ▶ ICON-2: Carbo vs Cis/Cyclo/Doxorubicin (CAP)
kein Vorteil, Toxizität ↑
- ▶ AGO: Carbo/Taxol vs Carbo/Taxol/Epirubicin
kein Vorteil, Toxizität ↑ (du Bois, JCO 2006, 24(7):1127-1135)
- ▶ EORTC/NCIC: Carbo/Taxol vs Carbo/Taxol/Epi
Toxizität ↑
- ▶ Hochdosis Cyclo/Epirubicin/Cisplatin: **kein Vorteil** (DFS 15,9 vs. 14,8 mo)
Ray-Coquard, Br J Cancer 2007 Nov 5;97(9):1200-5. Epub 2007 Oct 9
- ▶ GOG0182-ICON 5: Carbo/Taxol vs Carbo/T/Gem vs Carbo/T/LipoDox vs Carbo/Gem –Carbo/T vs Carbo/Topo –Carbo/T
kein Vorteil, Toxizität (Bookman JCO 2009, 1419-1425)

GCIG Intergroup study (AGO-OVAR/GINECO/NSGO) Protocol # AGO-OVAR 9

Strata:

* FIGO stage

* post-op residual tumor

* Surgery

Interval-surgery y/n

* Center

R
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N

Gemcitabine 800 mg/m² d1+8
iv

Paclitaxel 175 mg/m² 3 h iv

Carboplatin AUC 5 iv *

q 21 x 6

Paclitaxel 175 mg/m² 3 h iv

Carboplatin AUC 5 iv

q 21 x 6

AGO Ovarian Cancer Study Group (AGO-OVAR)

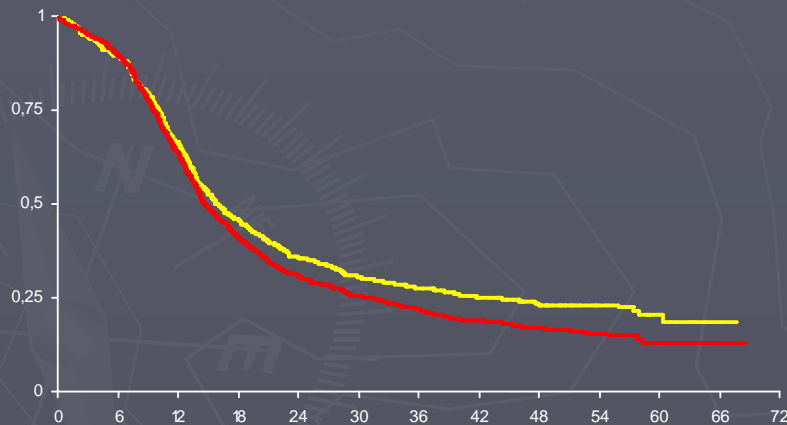
Progression-free (RECIST & GCIG CA125) and Overall Survival by Therapy within Stratum 2+3 (FIGO IIB-IV)

— TC 793 pts. / 588 evts.
median 16.0 [14.9-17.4] mos.

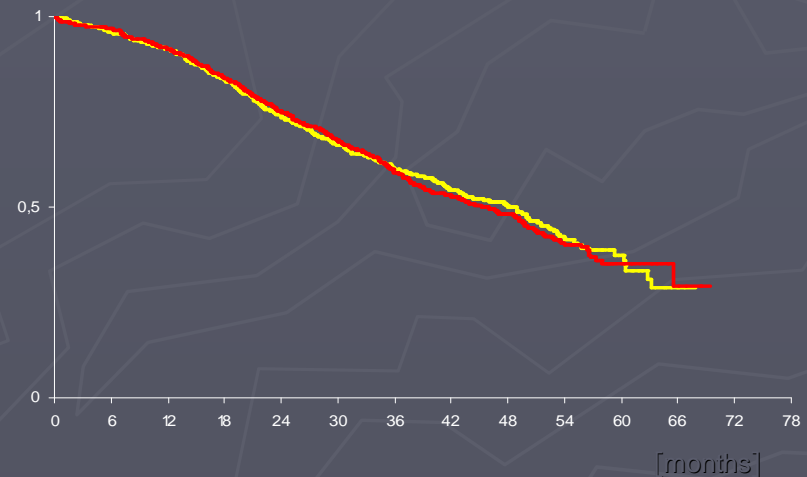
— TCG 774 pts. / 629 evts.
median 14.7 [14.0-15.9] mos.

— TC 793 pts. / 401 evts.
median 48.9 [43.1-51.2] mos.

— TCG 774 pts. / 404 evts.
median 45.8 [40.0-49.5] mos.



HR = 1.17 [95% CI: 1.05-1.31]
p = 0.0065



HR = 1.03 [95% CI: 0.90-1.18]
p = 0.6955

SCOTROC 4

Carboplatin Fix vs Dosis Eskalation- „Intrapatient“

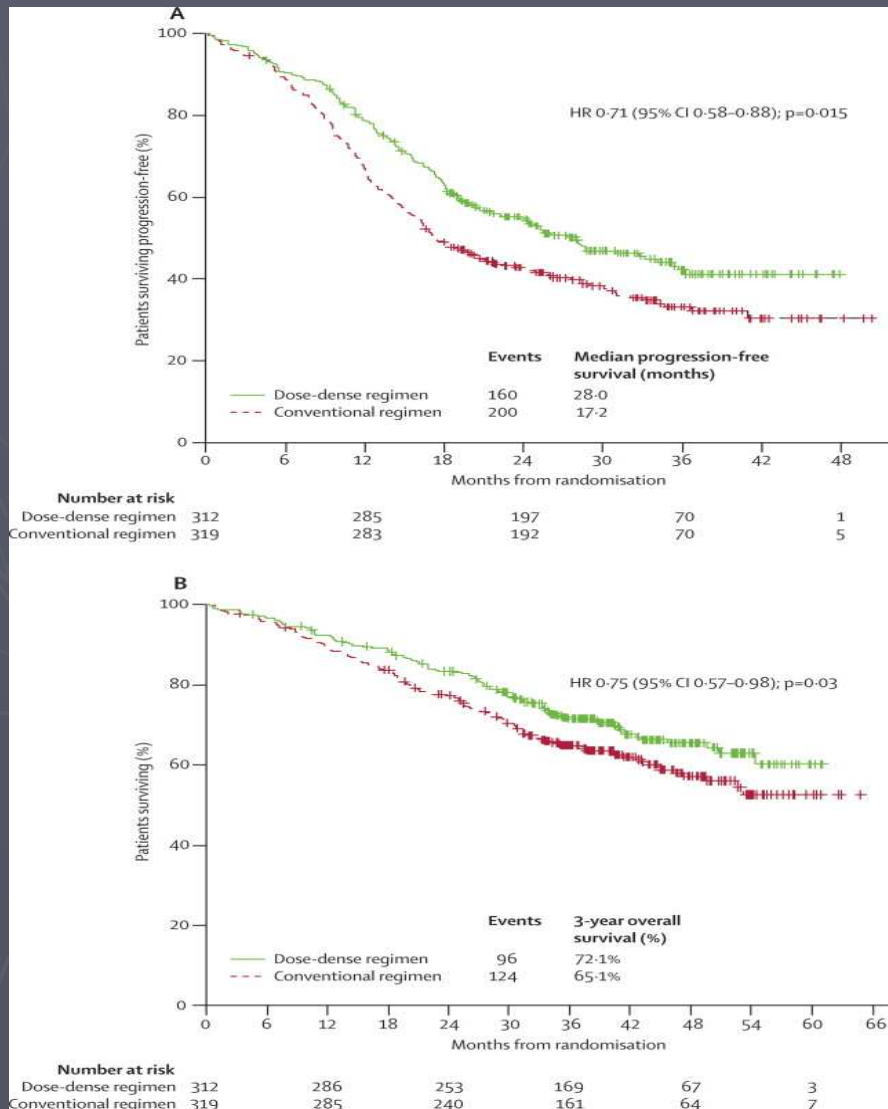
Patienten	937
Leading	SGCTG

ASCO 2009

Kein Vorteil für Dosiseskulation –
Studie geschlossen

Dose Dense- Prinzip

Katsumata The Lancet, 9698 ;1331 - 1338, 17 October 2009



- Carboplatin q 21 d
Paclitaxel d 1, 8, 15

- Carboplatin d1
Paclitaxel d1 q 21 Tage

PFS 28 mo vs 17,2 mo

3y OS 72,5% vs 65% p= 0,03

First-Line Therapie

Zusammenfassung

- ▶ Standardbehandlung
Carboplatin/Paclitaxel
- ▶ Docetaxel stellt eine Alternative zu Paclitaxel dar
- ▶ Kein Vorteil für Erweiterung um Epirubicin,
Gemcitabine, Topotecan
- ▶ Dose dense – Prinzip als neue Therapieform (?)

Erhaltungstherapie

- ▶ Rationale:
 - Progressionsfreies Überleben ~16 Monate
- ▶ SWOG 9326: Altretamin Phase II Alberts, Int J Gynaecol Can 224-8, 2004
 - PFS 28 Monate; OS 39 mo
- ▶ SWOG/GOG: Paclitaxel 12 Monate vs 3 Monate
 - PFS 28 Monate vs 21 Monate (p=0.0023)
 - OS ? (Vorzeitiger Abbruch der Studie) Markman et al. JCO, 2003:2460-2465
- ▶ Paclitaxel 6 Monate vs Observation:
 - kein Unterschied in PFS oder OS Conte et al. JCO, 2007 (18 Suppl): Abstr. 5505
- ▶ Y90-AK HMFG1 intraperitoneal – kein Vorteil
Verheijen, J Clin Oncol 24 (4): 571-8, 2006
- ▶ 4x Topotecan nach Standardtherapie (DFS 18,2 vs 18,5 mo) Pfisterer, J Natl Cancer Inst 98 (15): 1036-45, 2006
- ▶ TARCEVA-Trial (EORTC 55041): Erlotinib 150 mg tgl für 2 Jahre vs Observation; 835 Patienten; geschlossen; Ergebnisse ?

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Intraperitoneale vs intravenöse Chemotherapie

▶ Theorie: höhere Konzentration der Substanz in der Peritonealhöhle

▶ Positive Studie (Alberts GOG-104; NEJM 1996):

Cis ip / Cyclo iv vs Cis/Cyclo iv

N=546

CR: 47% vs 36%

medianes Überleben: 49 vs 41 Monate (p<.02)

▶ Positive Studie (Phase II Rothenberg, JCO 2003)

Taxol iv(d1)/Cis ip (d2)/ Taxol ip(d8)

medianes Überleben 51 Monate, 2y DFS 66%, 2y OS 91%

I.p.- vs i.v.-Chemotherapie

► Positive Studie (Markman GOG-14; JCO 2001):

2x Carbo iv → Cis ip / Taxol iv vs Cis/Taxol iv

N=462

PFS: 28 vs 22 mo (p=.01)

OS: 63 vs 52 mo (p=.05) **Toxizität!**

“Not recommended for routine use”

► Positive Studie (Armstrong GOG-172; NEJM 2006;354:34.43)

Cis/Taxol ip / Taxol iv vs Cis/Taxol iv

(Taxol 135 d1 24h/Cis 100 ip d2/Taxol 60 ip d8)

N=417,

PFS: 24 vs 19 mo (p=.029)

OS: 66 mo vs 50 mo (p=0,03)

Rezidiv-Risiko: HR 0,73

I.p.- versus i.v.-Chemotherapie

Toxizität

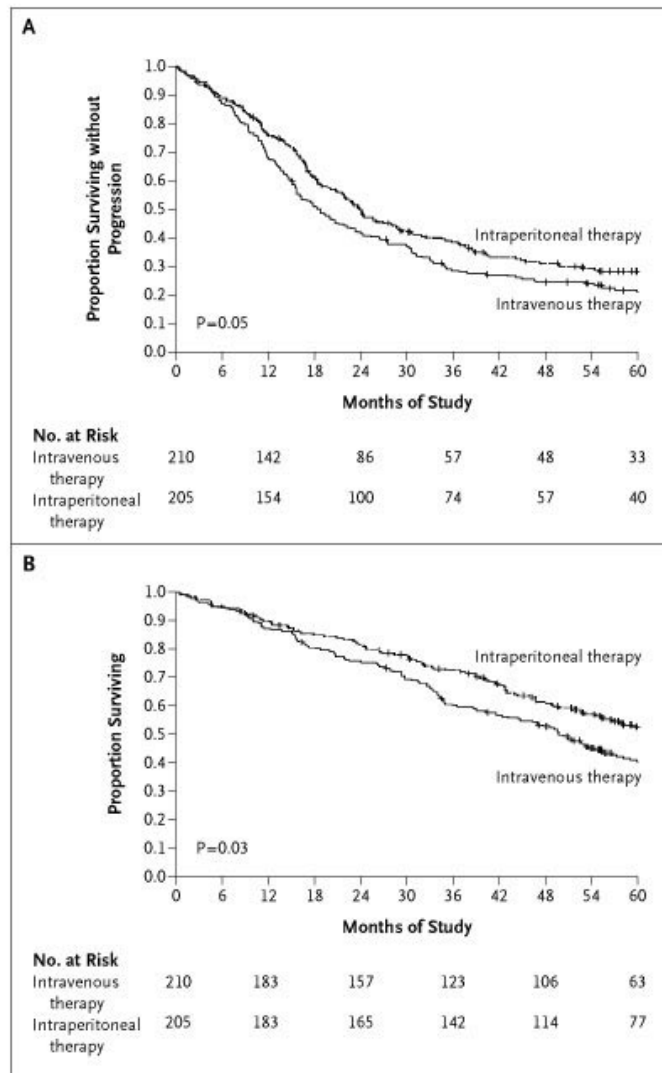
Nebenwirkung	i.v.-Gruppe %	i.p.-Gruppe %	P-Wert
Abdominelle Schmerzen	24	46	<0.001
Fieber	4	19	0.02
Leukopenie	64	76	<0.01
Fatigue	4	18	<0.001
Neurologische NW	9	19	0.001
Infektion	6	16	0.001

Intraperitoneale Chemotherapie

Taxol iv/Cis iv vs Taxol iv (d1)/Cis ip (d2)/Taxol ip (d8)

Armstrong, NEJM, 2006; 354:34-43

- PFS 18,3 vs 23,8 mo (p=0,05)
- Med OS 49,7 vs 65.6 mo (p=0,03)
- Nur 42% erhielten 6 Zyklen ip (86/205)
- 84/205 Pat erhielten 2 oder weniger Zyklen ip
- QoL Score 114,7 vs 103,3 (p<0,001) ! Vor 4. Zyklus
- QoL Score 127 vs 125 (p=0,65) nach 1 Jahr



•Cochrane Review:

21% Reduktion des Mortalitätsrisikos und Verlängerung des Krankheitsfreien Intervalls

•Carbo statt Cis ?

•Potential new standard?

—

•Andere Schemata – weniger Toxizität?

Intraperitoneale Therapie nach optimalem Debulking (Residuen < 1cm)

- ▶ **Metaanalyse I** Jaaback, Cochrane Database Syst Rev 2006 Jan 25;(1):CD005340
 - 8 Studien, 1819 Patientinnen
 - Signifikanter Vorteil für OS (Hazard Ratio 0,79) und DFS (HR= 0,79)

- ▶ **Metaanalyse II** Elit, Cancer 2007 Feb 15;109(4):692-702
 - 3 Phase III Studien, 4 weitere randomisierte Studien
 - Verbessertes Überleben von 8, 11 bzw. 16 Monaten
 - Survival Benefit für intraperitoneale Therapie (relative risk 0,88)

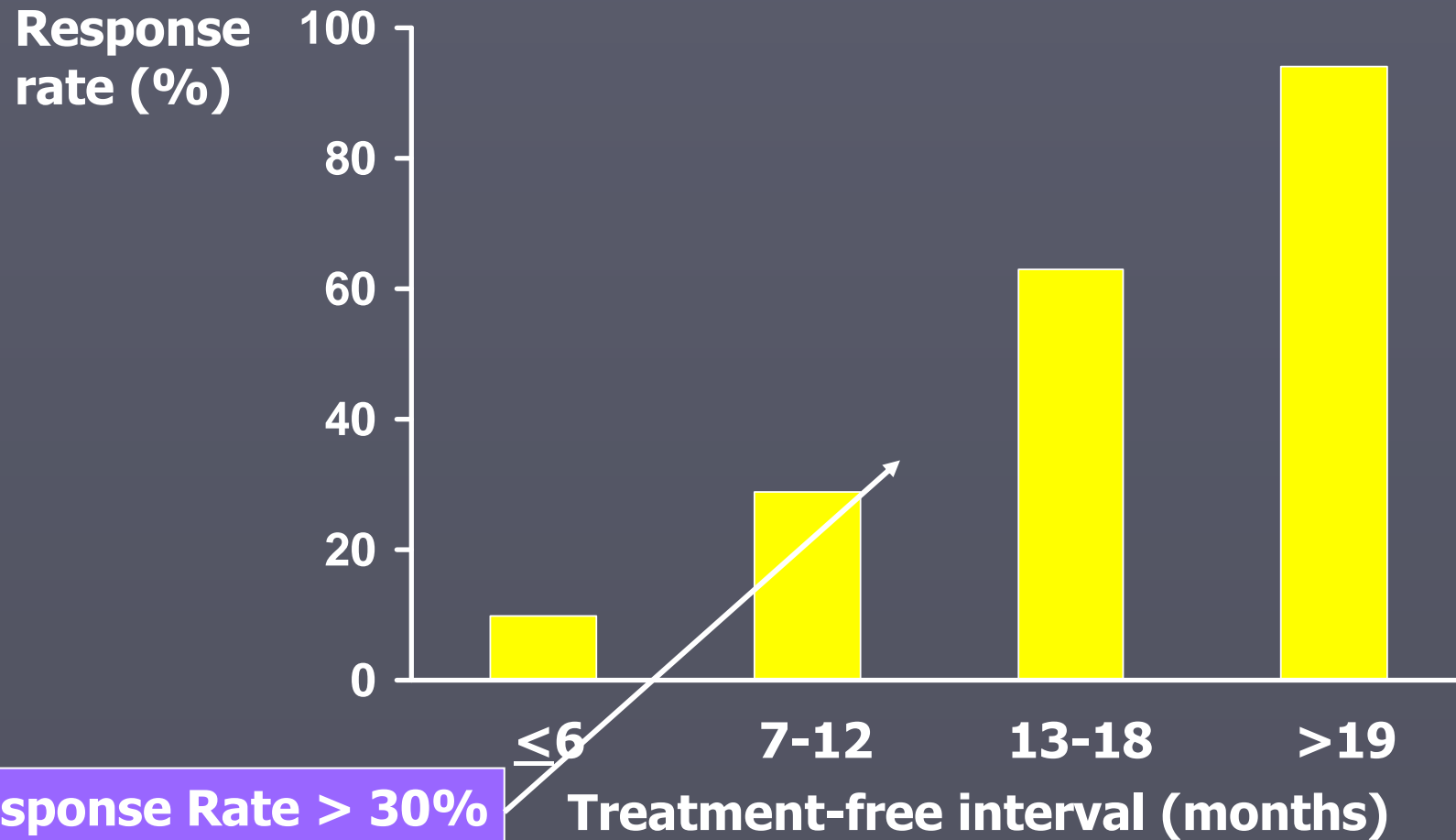
- ▶ **Metaanalyse III** Fung-Kee-Fung, Gynaecol Oncol 2007 Jun;105(3):747-56. Epub 2007 Mar 2
 - 8 Studien, OS Ergebnisse wie oben
 - Standards für die Behandlung erforderlich (Zentren)
 - Studien für das optimale Therapieregime

Internistische Therapie des Ovarialkarzinoms Fortgeschrittenes Stadium

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Rezidiv

Therapiefreies Intervall – “Platinsensitivität”



**Randomized MRC OV05/EORTC 55955 trial in
recurrent ovarian cancer: early treatment
based on increased serum CA125 alone
versus delayed treatment based on
conventional clinical indicators**

M.E.L. van der Burg¹, G.J. Rustin²

1Erasmus MC University Medical Center Rotterdam, Medical Oncology, Rotterdam, The Netherlands

2Mount Vernon Cancer Center, Medical Oncology, Middlesex, United Kingdom

- ▶ **OC patients (pts) in CR after first-line platinum-based chemotherapy and normal CA125**
- ▶ **Every 3 months (m) CA125 was measured and a clinical examination was performed. CA125 was blinded for the doctors and pts.**
- ▶ **At a rise of CA125 $>2\times$ upper limit of normal, pts were randomized to ET vs. DT. Second-line therapy was according to standard local practice in both arms.**
- ▶ **Primary endpoint was OS, secondary endpoints were time to third-line therapy or death and quality of life (QoL)**

ET = Early Treatment
DT = Delayed Treatment

- ▶ 96% ET vs. 88% DT pts received second-line therapy
- ▶ 64% ET vs. 51% DT received ≥ 6 cycles.
- ▶ Third-line therapy was administered in 67% ET vs. 54% DT, $p = 0.0001$.
- ▶ In the ET second-line therapy started median 4.8 m, and third-line median 4.7 m earlier (ET 12.5 m and DT 17.1 m, $p < 0.0001$).
- ▶ Median follow up of 57 mos: (370 deaths) - **no difference in OS** between the ET (25.7 m) and DT (27.1 m).
- ▶ No \uparrow in QoL by ET, median **time of good QoL** was 7.1 m for ET vs. 9.2 m for DT ($p = 0.20$)
- ▶ Time to first deterioration in global health score was 3.1 m for ET and 5.8 m for DT ($p = 0.001$) with significant disadvantage for **fatigue** 2.6 m ET vs. 6.1 m DT ($p < 0.0001$), role function 3.5 m ET vs. 6.0 m DT ($p < 0.006$) and social function 4.1 m ET vs. 8.6 m DT ($p = 0.003$).

Conclusion

- ▶ **No benefit from ET based on a raised serum CA125 alone.**
- ▶ **Survival in ET is the same as in DT at the cost of a shorter TFI, more chemotherapy and worse QoL.**

Kombination oder Monotherapie für platinsensitives Rezidiv

► ICON 4-AGO 2.2

(Lancet, June 21;2003):

- 802 Pat
- 2 Arme: Platin vs. **Platin+Paclitaxel**
- OS hazard ratio 0.82, p=0.02
- PFS hazard ratio 0,76 p=0.0004
- 1y PFS 40% vs 50%
- 2y OS 50% vs 57%
- Kein Einfluß auf die QoL

► GEICO (Ann Oncol May 2005)

- 81 Pat
- Carbo (AUC5) vs **Carbo/Taxol**
- Response Rate 50% vs 75,6%
- TTP 33,7w vs 49,1w
- Kein signifikanter Unterschied der QoL

Taxanfreie Rezidivtherapie platinsensitiv

(Ovar 2.5, AGO, Pfisterer et al. JCO, Sep 18, 2006)

- ▶ Rezidiv > 6 Monate, mind. Eine Vortherapie mit Platin oder Platin/Taxol, n = 365
- ▶ **Gemcitabine** (1000 d1 + 8 q 3 w)/**Carbo** AUC 4 q 3 w vs. Carbo (AUC 5 q 3 w)

- **PFS** **8,6 mo vs. 5,8 mo** (p=0,0031)
- **CR** **14,6% vs 6,2%**
- **PR** **32,6% vs 24,7%**
- **ORR** **47,2 vs. 30,2%** (p=0,0016)

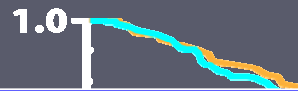
Neutropenie (Gr 3+4) 70,2% vs 12%

Verbesserte QoL (Neuropathie)

- ▶ LipoDox/Carbo Phase II: ORR 68%, PFS 11,6 mo; duBois, AGO-OVAR, Gynaec Oncol, 2007 Oct1

CLYPSO (Carbo/Taxol vs Carbo/Caelyx)

Progression-Free Survival (ITT)



CD	CP
----	----

Neutropenie	35%	46%	9.4
Schwere Neuropathie	5%	28%	(0.72, 94)
Alopezie	7%	84%	005
Hand/Fußs-Syndrom	13%	2%	.001
Thrombozytopenie	16%	6%	
Discontinuation	4,3%	14%	

Number at Risk

CD	467	397	188	60	20	4
CP	509	405	152	45	10	2

Substanzen in der Zweit- und Drittlinientherapie

👍 Platinsensitiv, >6 Mo therapiefreies Intervall:

👍 Carbo/Liposomales Doxorubicin

👍 Carbo/Paclitaxel

👍 Carbo/Gemcitabine

- Altretamin
- Epi-/Doxorubicin
- Liposomales Doxorubicin
- Etoposid
- Irinotecan
- 5-FU/LV
- Xeloda
- Ifosfamid
- Paclitaxel
- Docetaxel (weekly) ¹
- Topotecan
- Vinorelbin
- Gemcitabine
- Oxaliplatin

Substanzen in der Zweit- und Drittlinientherapie

👍 Platinsensitiv, >6 Mo therapiefreies Intervall:

👍 Carbo/liposomales Doxorubicin

👍 Carbo/Taxol

👍 Carbo/Gemzar

▶ Platin-resistent:

- Altretamin
- Epi-/Doxorubicin
- Liposomales Doxorubicin
- Etoposid
- Irinotecan
- 5-FU/LV
- Xeloda
- Ifosfamid
- Paclitaxel
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Platinrefraktäres Rezidiv

	Caelyx	Hycamtin	Taxol
Med. OS (wo) ^{1*}	60	56,7	
Platin-sensibel	108	70	
3y OS (%)	20,2	13,2	
Resp.Rate (%)	19,7	17	
OS (wo)		63 ^{2*}	53
TTP (wo)		19	15
Med. OS (wo)	47		56

1* Gordon, J Clin Oncol 19 (14): 3312-22, 2001

2* ten Bokkel Huinink, J Clin Oncol 15 (6): 2183-93, 1997

Review: Fung-Kee-Fung, Curr Oncol 2007, Oct;14(5):195-208

Welche Therapie Platinrefraktäres Rezidiv

▶ Taxan-naiv:

- Paclitaxel = Topotecan = Liposomales Doxo

▶ Taxan-vorbehandelt:

- Topotecan = Liposomales Doxo > Alkylanzien

(AGO Leitlinien 06/2009)

▶ Topotecan wenn LipoDox oder Paclitaxel nicht angebracht (Kosten)

(NICE, UK 2007)

Kombinations- vs Monotherapie

- ▶ Kombinationstherapie im platinsensitiven Rezidiv:
 - 👍 Ansprechrate besser
 - 👍 Überleben möglicherweise besser
 - 👎 Toxizität höher
- ▶ Kombinationstherapie bei refraktärer/resistenter Erkrankung:
 - 👍 Ansprechrate besser
 - ~ Überleben gleich
 - 👎 Toxizität höher

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Neue Therapien

▶ Monoklonale Antikörper:

- Trastuzumab ? (Erb-B2-Überexpression in 11% der Pat)
- Cetuximab (EGF-1-Überexpression)
- Bevacizumab (Anti-VEGF) Gynecol Oncol 2006 Aug:140-4;
- Orevogomab (OvaRex®) – CA-125
- Pertuzumab (Gordon, JCO 2006 Sep 10:4324-32) – Kombination mit Gemzar?

▶ Tyrosinkinase-Inhibitoren:

- Erlotinib (EGF-1-TKI)
- Sunitinib
- CI-1033 (EGF-1/2/3/4-TKI)
- ZD6474 (VEGF-TKI)

▶ Farnesyltransferase-Inhibitoren

▶ Tumorkvakzine

- ACA 125 (anti-anti-idiopathic antibody, ASCO 2005, # 5018)

▶ MMPs

▶ i.v./i.p.-Gentherapie

▶ MDR-Modulatoren (PSC 833)

▶ Angiogenesehemmer (Squalamin)

Neue Therapien

Bevacizumab

- ▶ **Bevacizumab Single-Agent** (GOG170D₁; Genetech AVF 2949₂):
 - RR 18% and 16% (vgl. kolorektal Ca.3% ECOG JCO 2005 (Suppl.) Abstr. 2)
 - 6-months PFS 39% and 27%
- ▶ **Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer.**
Chura J, Gynaecol Oncol 2007 Nov;107(2):326-330.
 - Cyclophosphamid 50mg/d po - Bevacizumab 10 mg/kg q 2 w
- ▶ **Bevacizumab and weekly taxane chemotherapy demonstrates activity in refractory ovarian cancer.** Cohn DE, Gynaecol Oncol 2006 Aug;102(2):134-9
- ▶ **Sustained progression-free survival with weekly paclitaxel and bevacizumab in recurrent ovarian cancer.** Hurt Gynaecol Oncol 2009

Is It Time for Some New Approaches for Treating Advanced Ovarian Cancer?

W.P. McGuire J Natl cancer Inst, Aug 2; 2006

- ▶ Kombination bekannter Zytostatika mit
 - Cetuximab
 - Bevacizumab:
 - **GOG 218** (Platin/Taxan x 6 Zyklen +/- Bevacizumab 15mg/kg q 3w/Placebo, 3.Arm extended Beva 16 Zyklen) - **OS**
 - **ICON7** (Platin/Taxan x 6 Zyklen +/- Bevacizumab 7,5mg/kg q 3w
danach Beva weiter für 12 w - **PFS**)
- ▶ Sorafenib
 - Sorafenib + Gemcitabine (Welch, JCO 2006, 24:276s Abstr 5084)
- ▶ Sunitinib
- ▶ Erlotinib

The real challenge, however, remains with screening and early diagnosis.

When diagnosed in stage I, more than 90% of patients have longer than 10 years of disease-free survival. Symptoms are non-specific, such as abdominal bloating, loss of appetite, and dysuria.

Screening with a combination of serum cancer antigen 125 and transvaginal ultrasonography is recommended in women at high risk, such as carriers of the *BRCA1* mutation. General screening in postmenopausal women is currently being assessed in the UK Collaborative Trial of Ovarian Cancer Screening due to end in 2011.

Major progress in ovarian cancer will only be made when the disease is diagnosed early.

Editorial, The Lancet, Oct 2009