

Case #2—First-Line Systemic Therapy for Ovarian Cancer

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First-Line Systemic Therapy for Ovarian Cancer

- **39-year-old woman**
- **Stage IIC clear cell G3 ovarian cancer**
- **Optimal cytoreduction**
- **Good performance status**
- **Concern about prognosis and toxicity**

Options to Consider

- **Paclitaxel + carboplatin regimen**
- **Paclitaxel weekly (dose-dense) + carboplatin**
- **Docetaxel + carboplatin regimen**
- **Pegylated liposomal doxorubicin + carboplatin regimen**
- **Gemcitabine + carboplatin + paclitaxel regimen**
- **Clinical trial of chemotherapy and bevacizumab if available**

What I Would Recommend

- **Paclitaxel + carboplatin regimen**
- **Paclitaxel weekly (dose-dense) + carboplatin**
- **Docetaxel + carboplatin regimen**
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Other Reasonanble Options

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- Paclitaxel weekly (dose-dense) + carboplatin
- Docetaxel + carboplatin regimen
- **Pegylated liposomal doxorubicin + carboplatin regimen**
- Gemcitabine + carboplatin + paclitaxel regimen
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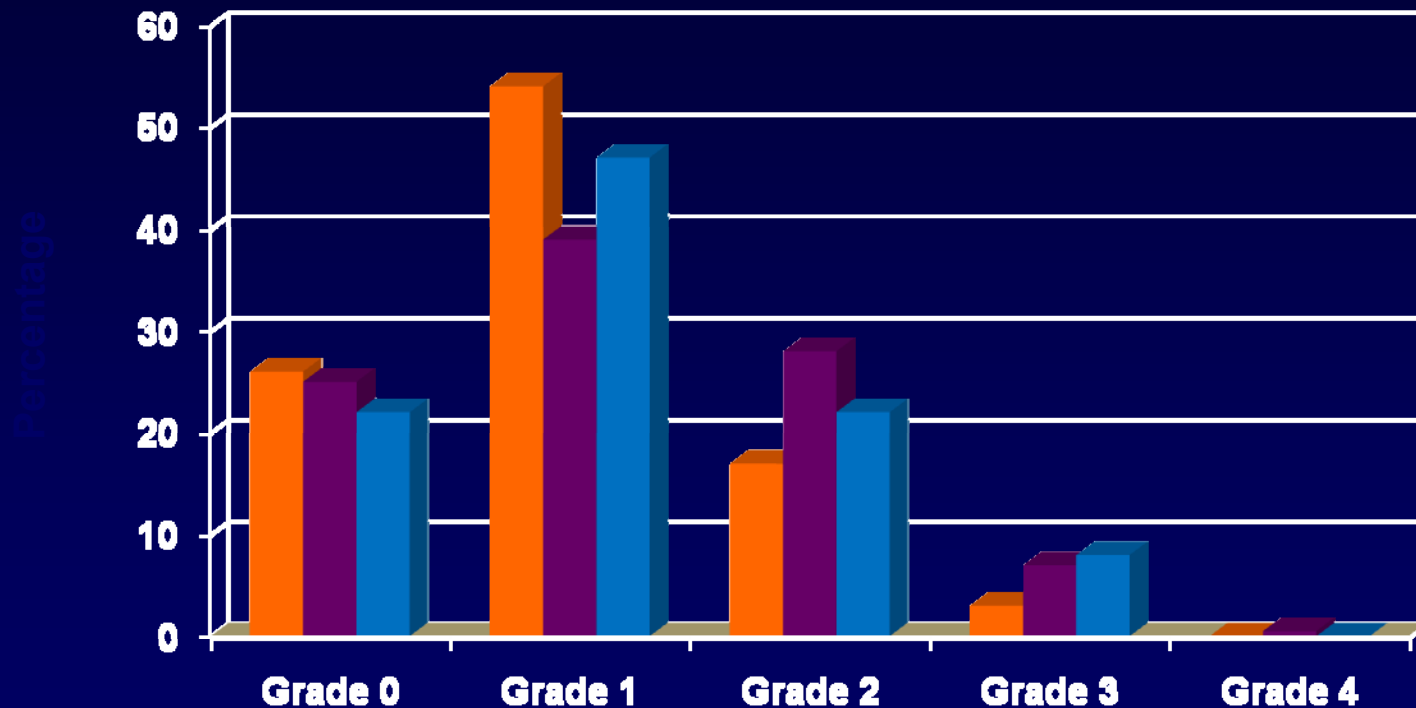
Current Standard: Paclitaxel + Carboplatin

- 3rd International Ovarian Cancer Consensus Conference (3 - 5 September 2004, Black Forest, Germany)
- The recommended standard comparator for trials on medical treatment in advanced ovarian cancer (FIGO IIB-IV) is **carboplatin-paclitaxel**
- The recommended regimen is **carboplatin with a dose of AUC 5 - 7.5 and paclitaxel 175 mg/m²/3h given every three weeks for 6 courses**

Advanced Ovarian Cancer Improving Standard Approach

- **Currently, paclitaxel/carboplatin standard provides:**
 - Response rate of 70% to 80+%
 - Progression-free survival of 16-20+ months
 - Overall survival of 31- ~60 months
 - Majority (three-quarters) relapse and eventually succumb to disease
- **Neurotoxicity, fatigue and alopecia problematic for patients**
- **Need new strategies to improve outcome and tolerability**

Neurotoxicity During First-Line Paclitaxel/Carboplatin Chemotherapy



■ Neijt JP, et al. *J Clin Oncol.* 2000;18(17):3084-3092.

■ du Bois A, et al. *J Natl Cancer Inst.* 2003;95(17):1320-1329.

■ Vasey PA, et al. *J Natl Cancer Inst.* 2004;96(22):1682-1691.

Paclitaxel Weekly (Dose-Dense) + Carboplatin

Japanese Gynecologic Oncology Group Trial

FIRST LINE

Stage II – IV

OVARIAN CANCER

(including primary peritoneal fallopian tube)

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Paclitaxel 180 mg/m² day 1 q 3w

Carboplatin AUC 6 day 1 6 – 9 cycles

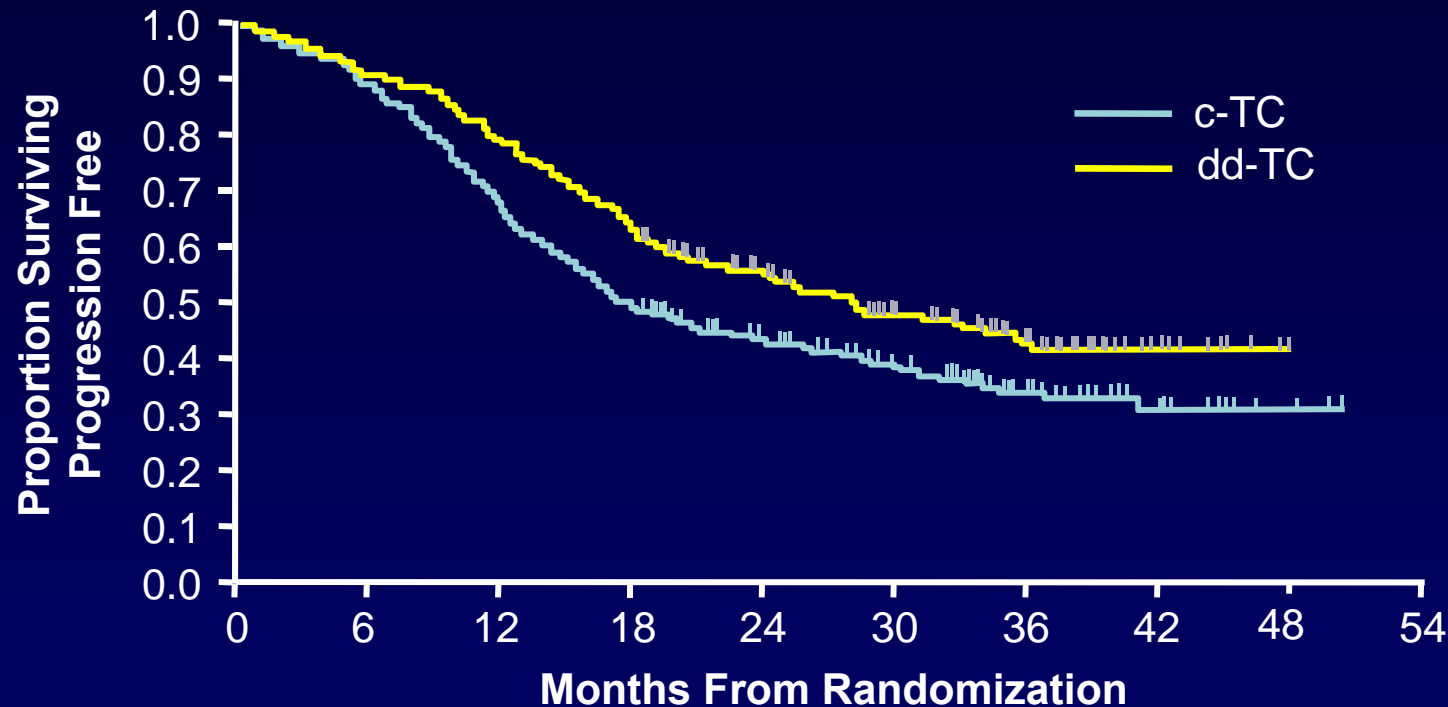
Paclitaxel 80 mg/m² days 1,8,15 q 3w

Carboplatin AUC 6 day 1 6 – 9 cycles

Primary endpoint: PFS

Total accrual: 637 patients

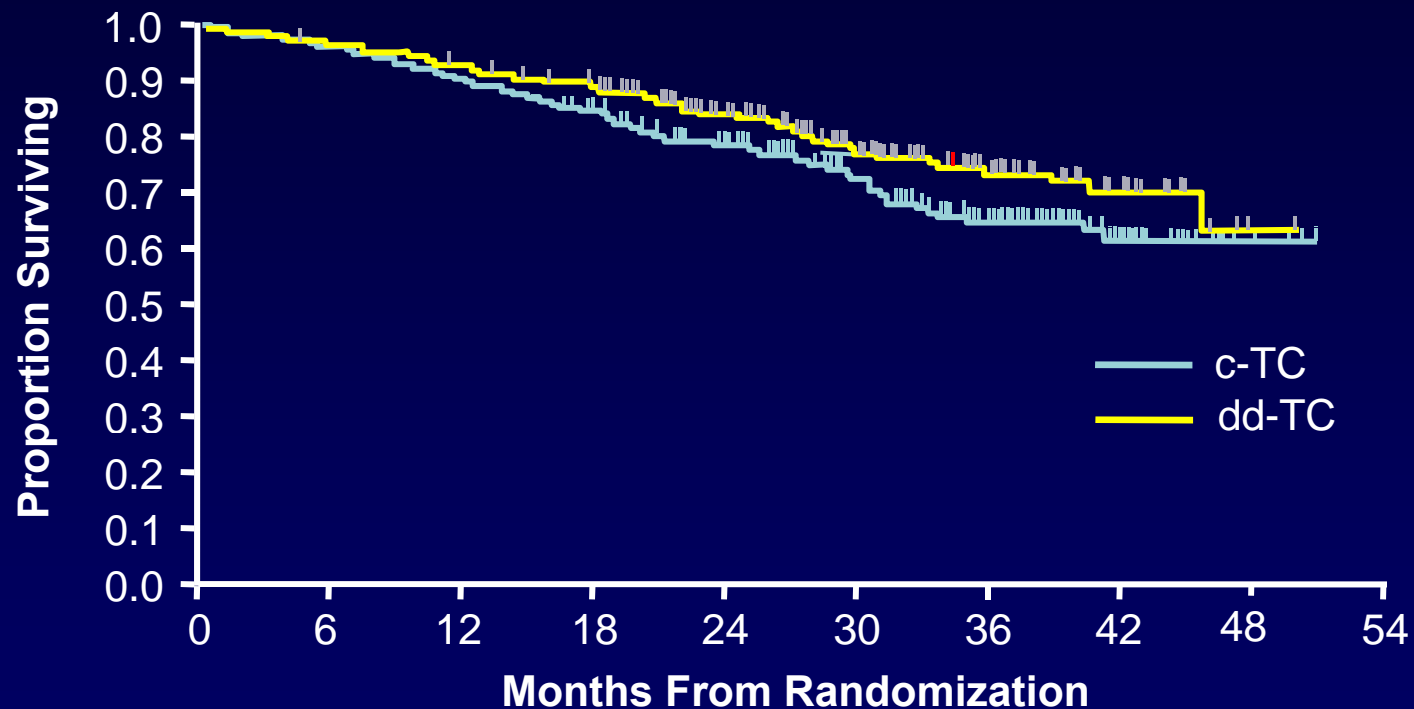
Standard Pac/Carbo vs Weekly Pac/Carbo in First-Line Treatment: Progression-Free Survival



Treatment	n	Event	Median PFS, mos	P Value	HR	95%CI
c-TC	319	200	17.2			
dd-TC	312	160	28.0	.0015	0.714	0.581-0.879

Katsumata N, et al. *Lancet*. 2009;374(9698):1331-1338.

Standard Pac/Carbo vs Weekly Pac/Carbo in First-Line Treatment: Overall Survival



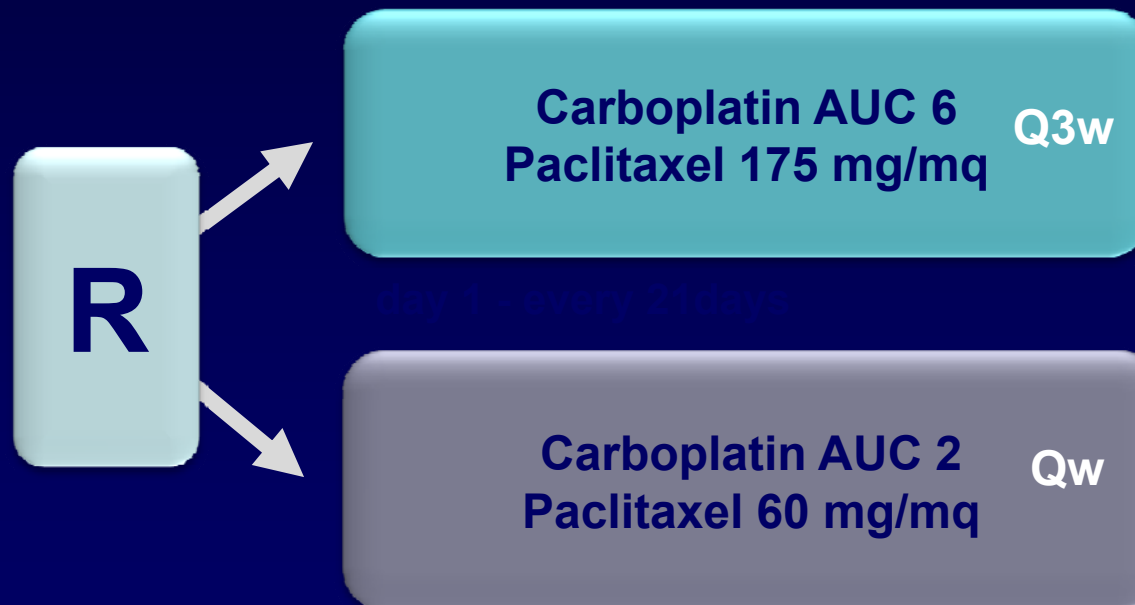
Treatment	n	Event	2-Year Survival, %	P Value	HR	95%CI
c-TC	319	95	77.7			
dd-TC	312	70	83.6	.0496	0.735	0.540-1.000

Katsumata N, et al. *Lancet*. 2009;374(9698):1331-1338.

MITO-7 Phase III Trial

First-Line Weekly Carboplatin and Paclitaxel
vs Every 3 Weeks Carboplatin/Paclitaxel in Patients with Ovarian Cancer

Aim of the trial is to compare the two schedules in
terms of quality of life and PFS



Primary endpoint: QoL, PFS (amendment)

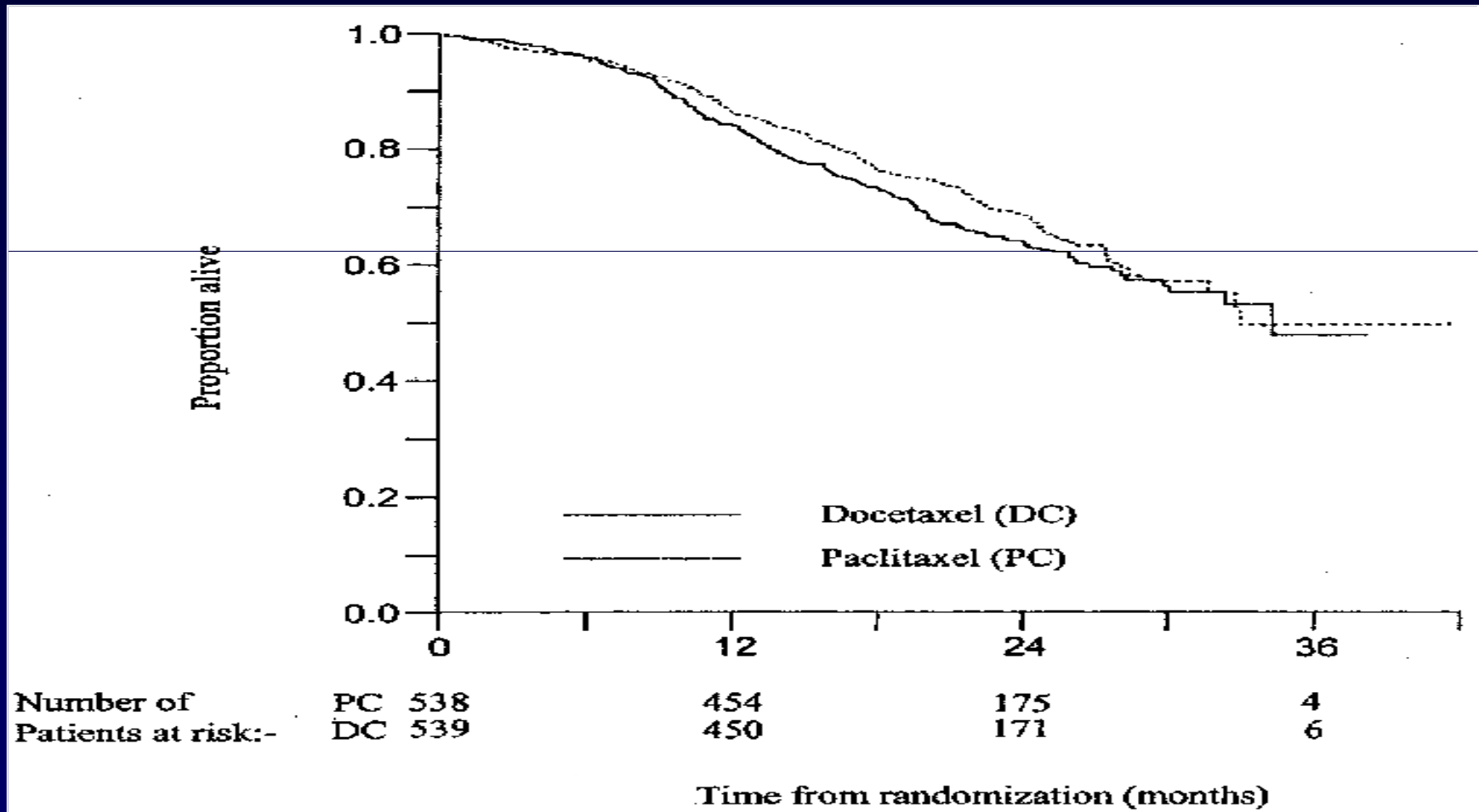
Secondary endpoints: OS, ORR, toxicity

Estimated accrual: 400 patients

Docetaxel + Carboplatin Regimen

- Phase III Randomized Trial of Docetaxel–Carboplatin Versus Paclitaxel–Carboplatin as First-Line Chemotherapy for Ovarian Carcinoma
- Higher G3/4 myelosuppression
- Less neurotoxicity
 - G2-4 neurosensory toxicity: Doce/carbo vs pacli/carbo: 11% vs 30% ($P = .001$)
 - G2-4 neuromotor toxicity: Doce/carbo vs pacli/carbo: 3% vs 7% ($P = .001$)
- Docetaxel–carboplatin **appears to be similar to paclitaxel–carboplatin** in terms of progression-free survival and response, although longer follow-up is required for a definitive statement on survival. Thus, docetaxel–carboplatin represents an alternative first-line chemotherapy regimen for patients with newly diagnosed ovarian cancer

SCOTROC 1: Survival



Vasey PA, et al. *J Natl Cancer Inst.* 2004;96(22):1682-1691.

Gemcitabine + Carboplatin + Paclitaxel Regimen

- A randomized, phase III study (AGO-OVAR-9, GINECO-TCG, NSGO-OC-0102): Gemcitabine-paclitaxel-carboplatin (TCG) versus paclitaxel-carboplatin (TC) as first-line treatment of ovarian cancer (OC): Survival of FIGO stage I-IIA patients
- PFS - HR = 0.90 [95% CI: 0.47-1.72]
- OS - HR = 2.19 [95% CI: 0.75-6.41]
- Greater hematologic toxicity in study arm
- **Addition of G to TC did not improve efficacy in patients with stage I-IIA ovarian cancer. The addition of G to TC in patients with first diagnosis of ovarian cancer cannot be recommended**

GCIIG Intergroup Study: AGO-OVAR / GINECO / NSGO Study Design

Stratification

- Center
- Interval debulking surgery planned (yes/no)
- FIGO stage and tumor residuals
 - Stratum 1 FIGO IA/IB G3 or IC-IIA
 - Stratum 2 FIGO IIB - IIIC + Tumor Residual \leq 1cm
 - Stratum 3 FIGO IV or Tumor Residual $>$ 1 cm

1st ENDPOINT

- Overall survival in stratum 2+3

2nd ENDPOINT

- PFS in stratum 2+3
- OS e PFS in stratum 1
- OS e PFS in all stratum
- Response rate
- Toxicity (NCI/CTC grade 3/ 4)
- EORTC QLQ-C 30, QLQ-OV 28

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Gemcitabine	800 mg/mq	d1+8
Paclitaxel	175 mg/mq	d1
Carboplatin	AUC5*	d1

q21 x 6

Paclitaxel	175 mg/mq	d1
Carboplatin	AUC5	d1

q21 x 6

AGO Ovarian Cancer Study Group (AGO-OVAR)

* evaluated in preceding Phase II Study protocol # AGO-OVAR 8

Herrstedt J, et al. *J Clin Oncol.* 2009;27(18S): Abstract LBA5510.

ADDING THIRD CYTOSTATIC DRUG TO TC		RESULT
Triplet combination	Gemcitabine AGO ,GINECO, NSGO GOG,ANZGOG-MRC	Negative
	Epirubicin AGO - GINECO NSGO EORTC NCIC-GEICO	Negative
	Peg-lip dox GOG ,ANZGOG MRC	Negative
Sequential doublet	Gemcitabine GOG,ANZGOG-MRC	Negative
	Topotecan NCIC EORTC GEICO GOG,ANZGOG-MRC	Negative
Sequential single	Topotecan AGO GINECO MITO	Negative

1. du Bois A, et al. *J Clin Oncol.* 2006;24(7):1127-1135.
2. Kristensen GB, et al. *J Clin Oncol.* 2004;22(14S): Abstract 5003.
3. Bookman MA, et al. *J Clin Oncol.* 2009;27(9):1419-1425.
4. Hoskins PJ, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract LBA5505.
5. Pfisterer J, et al. *J Natl Cancer Inst.* 2006;98(15):1036-1045.

Herrstedt J, et al. *J Clin Oncol.* 2009;27(18S): Abstract LBA5510.

Pegylated Liposomal Doxorubicin + Carboplatin Regimen

- Carboplatin plus paclitaxel (CP) versus carboplatin plus stealth liposomal doxorubicin (CLD) in patients with advanced ovarian cancer (AOC): MITO-2 Trial
- 820 patients randomized
- Stage IC-IV
- Median follow up 35 months
- 530 events for PFS
- 269 deaths

MITO-2 STUDY: Role of Pegylated Liposomal Doxorubicin

Randomized phase III
first-line treatment of patients
with advanced ovarian cancer

Stratification:

- Center
- PS (0-1, 2)
- Stage (IC, II, III, IV)
- Residual disease after surgery (absent, ≤ 1 cm, >1 cm, no surgery)

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Control arm

Carboplatin AUC 5, day 1
Paclitaxel 175 mg/m², day 1

Treatment repeated every 21 days, for 6 cycles

Experimental arm

Carboplatin AUC 5, day 1
PLD 30 mg/m², day 1

Treatment repeated every 21 days, for 6 cycles

Primary endpoint: PFS

Secondary endpoints: OS, ORR (RECIST), toxicity, quality of life

MITO-2: Toxicity Comparison

	Any Grade			Severe (G \geq 3)		
	C+P	C+PLD	P*	C+P	C+PLD	P*
Anemia	59%	68%	.007	4%	10%	<.001
RBC transfusions				2%	6%	.002
Neutropenia	73%	80%	.04	49%	43%	.09
Febrile neutropenia				2%	1%	.21
Thrombocytopenia	19%	48%	<.001	2%	16%	<.001
Platelet transfusions				0.3%	2%	.06
Diarrhea	13%	6%	<.001	1%	-	.25
Hair loss	63%	14%	<.001			
Skin toxicity	6%	20%	<.001	-	2%	.01
Stomatitis	9%	20%	<.001	0.3%	0.5%	.62
Neurotoxicity	47%	15%	<.001	3%	0.2%	.004

C+P: carboplatin + paclitaxel, 399 patients; C+PLD: carboplatin + PLD, 386 patients

*Chi square or Fisher exact test as appropriate

Pignata S, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5508.

Objective Response (RECIST)

Target Lesions	C+P (n = 156)	C+ PLD (n = 134)	<i>P</i> (χ^2)*
Objective response	92 (59%)	76 (57%)	.70
Complete response	24 (15%)	22 (16%)	
Partial response	68 (44%)	54 (40%)	
No response	64 (41%)	58 (43%)	
Stable disease	45 (29%)	41 (31%)	
Progressive disease	9 (6%)	7 (5%)	
Not evaluated	10 (6%)	10 (7%)	

*Objective response vs no response

Response: Nontarget Lesions and CA125

Nontarget Lesions	C+P (n = 83)	C+ PLD (n = 99)	<i>P</i> (χ^2)*
Complete response (CR)	27 (33%)	29 (29%)	.64
No CR/ No PD	46 (55%)	48 (48%)	
Progressive disease	2 (2%)	4 (4%)	
Not evaluated	8 (10%)	18 (7%)	

*Complete response vs not

Elevated CA125 Only	C+P (n = 88)	C+ PLD (n = 80)	<i>P</i> (χ^2)**
CA125 normalized	73 (83%)	69 (86%)	.56

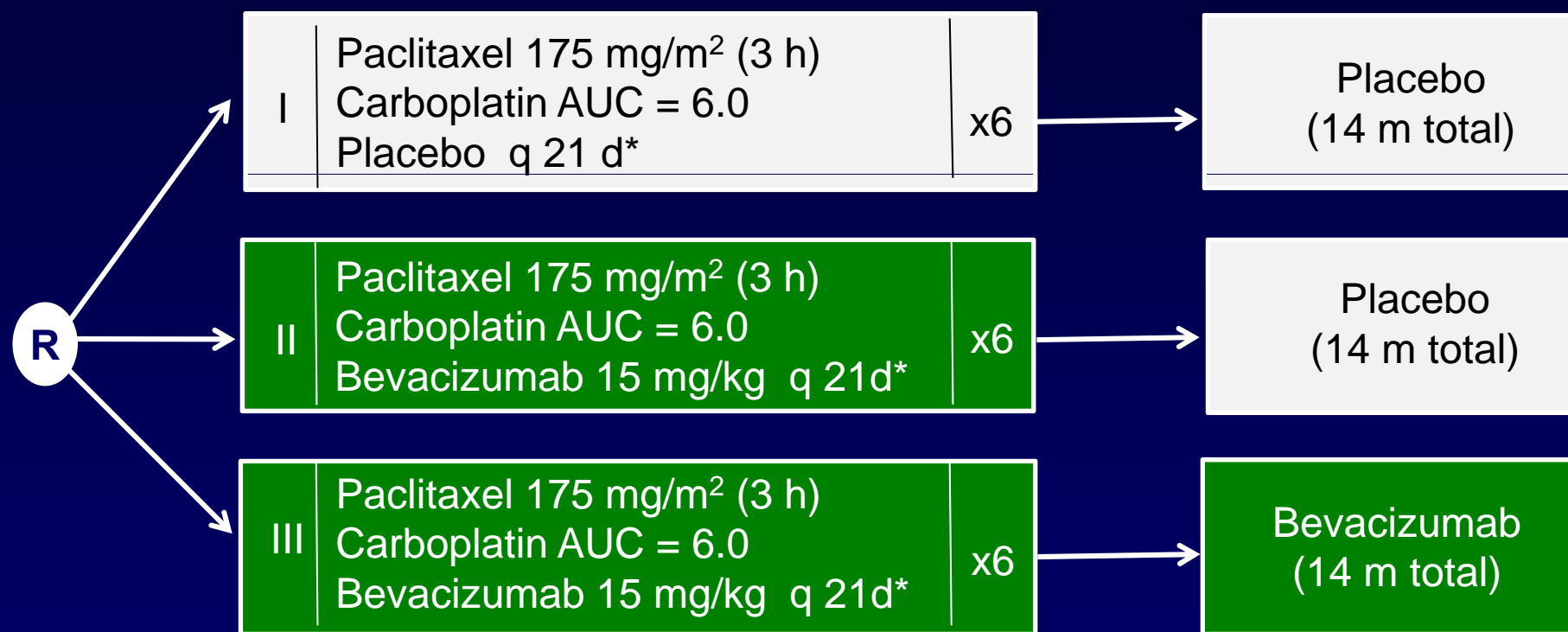
**CA125 normalized vs not

Clinical Trial of Chemotherapy and Bevacizumab (If Available)

- **GOG #218**
- **ICON 7**
- **GOG #252**

GOG218: Ovarian (Stage III-IV)

- Epithelial ovarian or primary peritoneal cancer
- Suboptimal cytoreduction
- Leading GOG
- Participating: ECOG, NCCTG, NSABP, SWOG



*starting with C2

Open:	Sept-05
Closed:	2009
Target accrual:	2000 patients (3Y)

Study Chair: Robert A. Burger, MD

GOG 218: Press Release Feb 2010

- The combination of bevacizumab and chemotherapy followed by maintenance use of bevacizumab alone **increased progression-free survival compared to chemotherapy alone**
- A preliminary assessment of safety noted adverse events previously observed in pivotal trials of bevacizumab
- Data from the study will be submitted for **presentation at ASCO 2010**

ICON 7 Bevacizumab Trial MRC Lead Group

Stratification factors:

- Stage
- Residual disease status
- Country

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Carboplatin AUC 6
Paclitaxel 175 mg/m²
Bevacizumab 7.5 mg/m²

q 21 x 6 cycles

Bevacizumab 7.5 mg/m²

q 21 x 12 cycles

Carboplatin AUC 6
Paclitaxel 175 mg/m²

q 21 x 6 cycles

Observation

N = 1520

- Stage IIB-IV patients
- High-risk stage I/IIA patients
- OC, FT, PPC

GOG 252: IP Chemotherapy and Bevacizumab

Regimen I: pacli/carbo _{IV} bevacizumab iv	Paclitaxel 80 mg/m ² IV wkly x 3
	Carboplatin AUC 6 IV every 3 wks
	Repeated for 6 cycles
Regimen II: pacli/carbo _{IP} bevacizumab iv	Paclitaxel 175 mg/m ² IV over 3 hrs on Day 1
	Carboplatin AUC 6 IP on Day 1
	Repeated every 3 wks for 6 cycles
Regimen III: Pacli/cisp _{IP} /pacli _{IP} bevacizumab iv	Paclitaxel 135 mg/m ² IV over 3 hrs on Day 1
	Cisplatin 75 mg/m ² IP on Day 2
	Paclitaxel 60 mg/m ² IP on Day 8
	Repeated every 3 wks for 6 cycles

Each of these regimens are to include : **Bevacizumab 15 mg/kg IV every 3 wks cycles 2-6 and then bevacizumab 15 mg/kg IV cycles 7-22**

Recommended Follow-Up When NED

- Routine measurement of CA125
- Measurement of CA125 only if symptoms occur

MRC OV05/EORTC 55955: Early Treatment Based on CA125 Level Alone vs Delayed Treatment

Ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA125

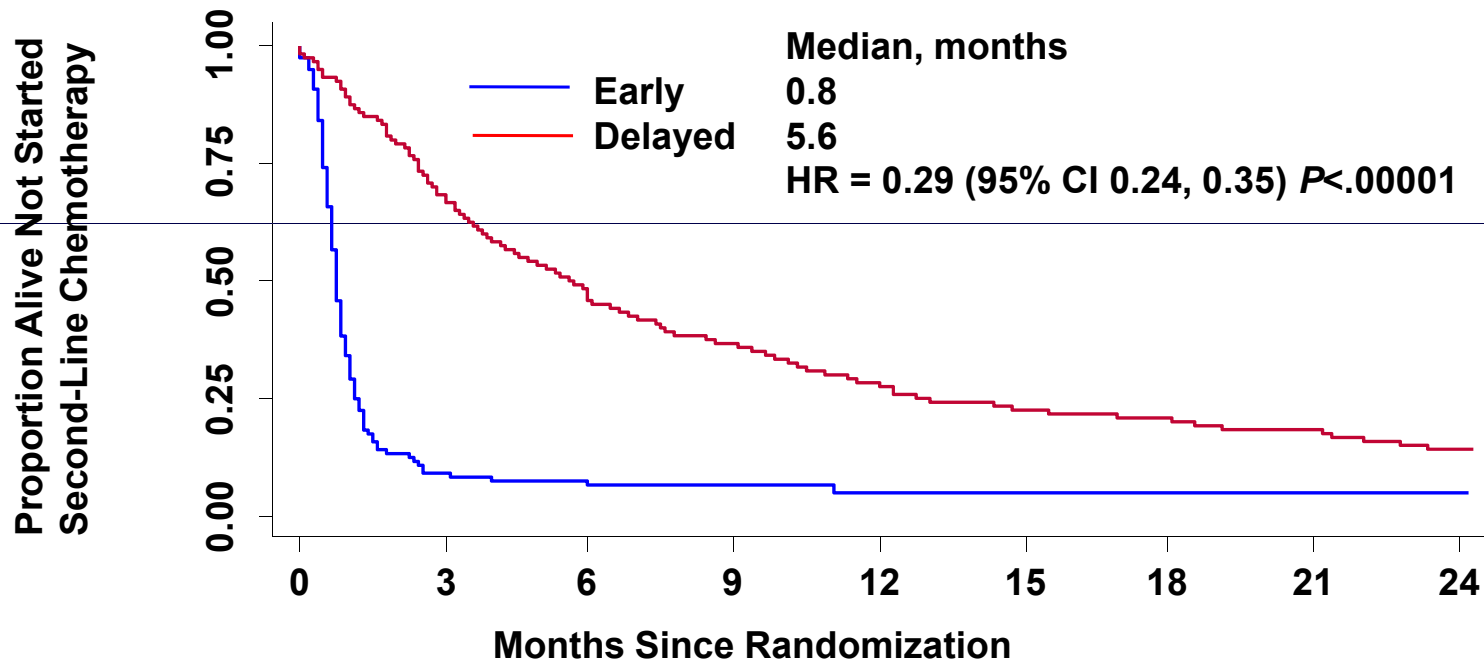
REGISTER (n = 1442)
Blinded CA125 measured every 3 months

CA125 > 2 x upper limit of normal
RANDOMIZED (N = 529) (37%)

Early treatment (N = 265)
Clinician and patient informed

Delayed treatment (N = 264)
Clinician not informed, treatment delayed until clinically indicated

Time from Randomization to Second-Line Chemotherapy



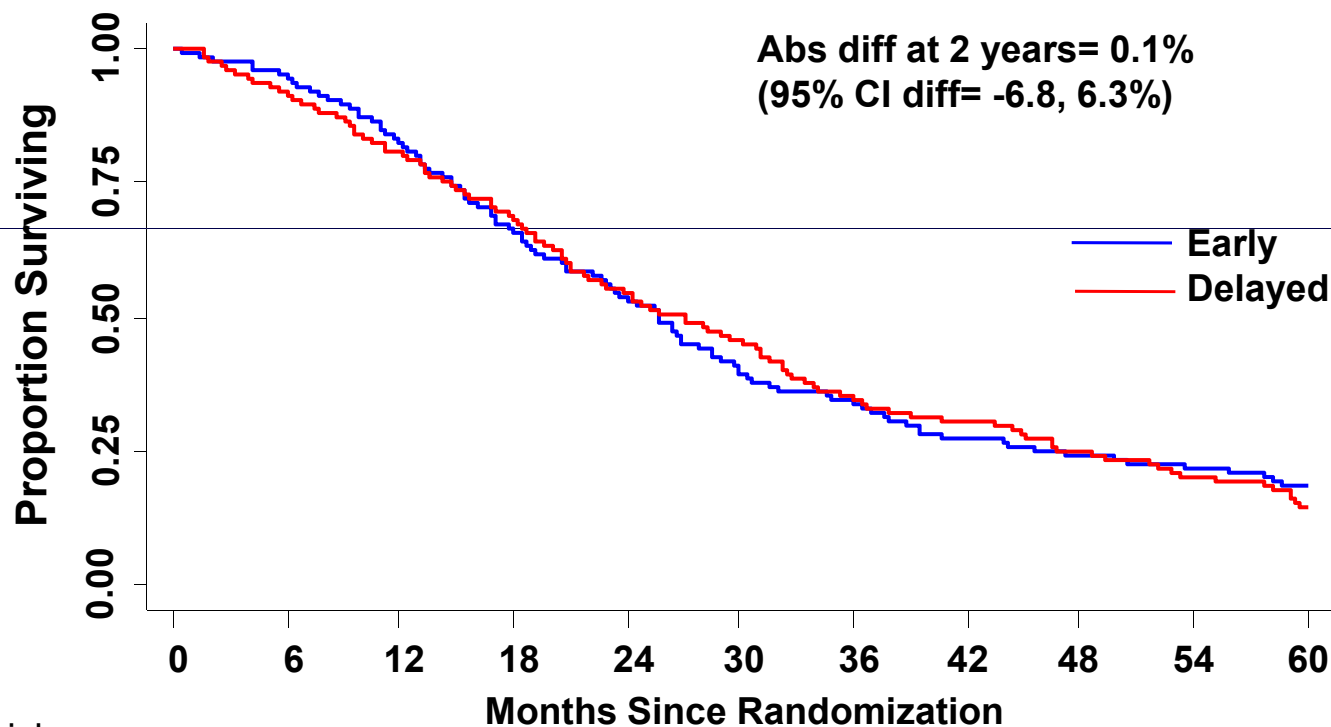
Number at risk

Early	265	23	16	14	11	11	10	10	9
Delayed	264	177	116	91	69	56	49	42	33

Overall Survival

HR = 1.00 (95%CI 0.82-1.22) P = .98

Abs diff at 2 years = 0.1%
(95% CI diff = -6.8, 6.3%)



Number at risk

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

Recommended Follow-Up When NED

- There is no survival benefit from early treatment based on a raised serum marker level alone, and therefore no value in the routine measurement of CA125 in the follow-up of ovarian cancer patients

My Opinion

- Routine measurement of CA125
- **Measurement of CA125 only if symptoms occur**