

Expanding Options in the First-Line Setting

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Ovarian Cancer First-Line Chemotherapy

1988-2008

- Cisplatin**
- Cisplatin/paclitaxel**
- Carboplatin/paclitaxel**

The Paclitaxel Era! GOG 111

The New England Journal of Medicine

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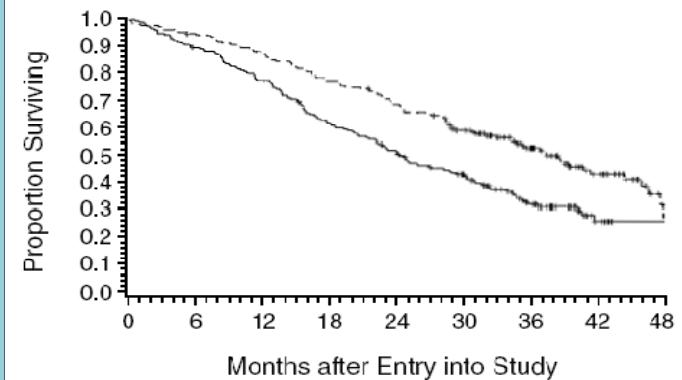
Volume 334

JANUARY 4, 1996

Number 1

CYCLOPHOSPHAMIDE AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN IN PATIENTS WITH STAGE III AND STAGE IV OVARIAN CANCER

WILLIAM P. MCGUIRE, M.D., WILLIAM J. HOSKINS, M.D., MARK F. BRADY, B.S., PAUL R. KUCERA, M.D.,
EDWARD E. PARTRIDGE, M.D., KATHERINE Y. LOOK, M.D., DANIEL L. CLARKE-PEARSON, M.D.,
AND MARTIN DAVIDSON, M.D.



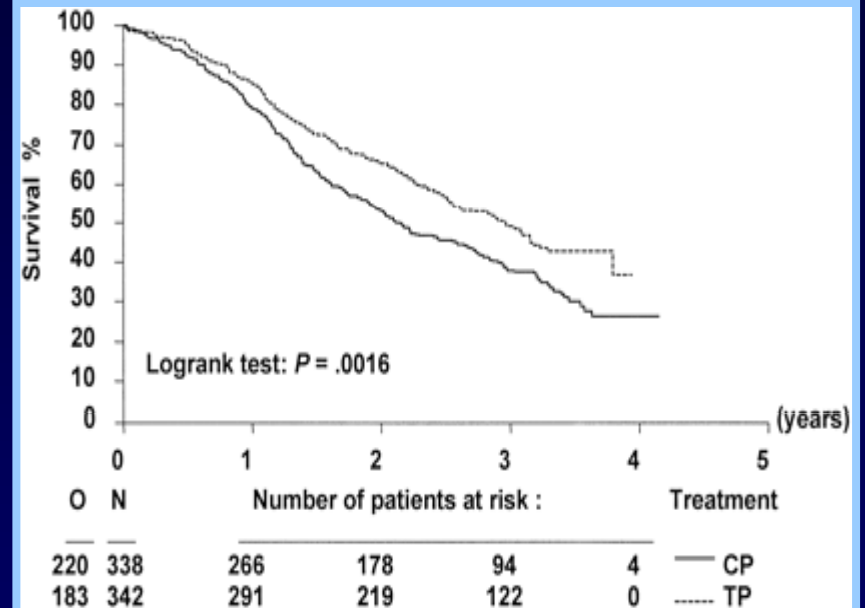
Treatment:	No. Alive	No. Dead	Total	Median Survival (mo)
— Cisplatin + cyclophosphamide	65	137	202	24
- - - Cisplatin + paclitaxel	86	98	184	38

McGuire WP, et al. *N Engl J Med.* 1996;334(1):1-6.

The Paclitaxel Era! OV 10

Randomized Intergroup Trial of Cisplatin–Paclitaxel Versus Cisplatin–Cyclophosphamide in Women With Advanced Epithelial Ovarian Cancer: Three-Year Results

Martine J. Piccart, Kamma Bertelsen, Keith James, Jim Cassidy, Constantino Mangioni, Ernst Simonsen, Gavin Stuart, Stan Kaye, Ignace Vergote, René Blom, Robert Grimshaw, Ronald J. Atkinson, Ken D. Swenerton, Claes Tropé, Mario Nardi, Janne Kaern, Salvatore Tumolo, Petra Timmers, Josée-Anne Roy, François Lhoas, Berit Lindvall, Monica Bacon, Angelo Birt, Joern Erik Andersen, Benny Zee, James Paul, Benoît Baron, Sergio Pecorelli



Neurotoxicity of Paclitaxel-Cisplatin

Grade	Cisplatin +	
	Paclitaxel 3 Hr	Paclitaxel 24 Hr
0	29	72
1	29	15
2	21	9
3	18	4
4	3	0

Connelly et al , *Gynecol Oncol.* 1996¹

Sensory	G3	14%
	G4	1%
Motor	G3	3%

OV 10 study-Piccart et al, *JNCI.* 2000²

1. Connelly E, et al. *Gynecol Oncol.* 1996;62(2):166-168. 2. Piccart MJ, et al. *J Natl Cancer Inst.* 2000;92(9):699-708.

Paclitaxel-Carboplatin (TC) vs Paclitaxel-Cisplatin (TP)

Trial	Treatment Arms	Reference	Patients	Results
AGO	T 185 vs T 185 P 75 C 6	Du Bois <i>JNCI</i> 2003 ¹	776 IIB-IV	TP = TC mPFS 19 v 17 mo
GOG-158	T 135 vs T 175 P 75 C 7.5	Ozlos <i>JCO</i> 2003 ²	840 III (<1cm)	TP = TC mPFS 19 v 21 mo
Danish- Dutch	T 175 vs T 175 P 75 C 5	Neijt <i>JCO</i> 2000 ³	208 IIB-IV	TP = TC mPFS 16 v 16 mo

1. du Bois A, et al. *J Natl Cancer Inst.* 2003;95(17):1320-1329. 2. Ozols RF, et al. *J Clin Oncol.* 2003;21(17):3194-3200. 3. Neijt JP, et al. *J Clin Oncol.* 2000;18(17):3084-3092.

Ovarian Cancer First-Line: Carboplatin-Paclitaxel Standard

- Consensus based on 3 phase III studies that compared:
 - Paclitaxel + carboplatin vs paclitaxel + cisplatin
 - Noninferiority studies
- Primary endpoint for noninferiority reached
- In addition, paclitaxel plus carboplatin was demonstrated superior in terms of
 - Ease of use
 - Quality of life
 - Lower toxicity

Ovarian Cancer First-Line: Carboplatin-Paclitaxel Standard

- **How improve the results?**
 - **Progression-free survival (PFS): 16-23 months**
 - **Overall survival (OS): 31-65 months**
 - **65% to 70% of patients requiring second-line treatment**

 - **Alopecia, fatigue, neurotoxicity....**

2000-2008 Phase III Strategies

- **Intraperitoneal (IP) chemotherapy**
 - GOG172
- **Optimizing paclitaxel efficacy**
 - JGOG study
- **Add new drugs**
 - GOG 182 – ICON5
- **New doublets**
 - MITO-2

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Development of Intraperitoneal Chemotherapy

- 1950s:** First use of IP chemotherapy for malignant ascites
- 1968:** Long-term peritoneal access device
- 1978:** Demonstration of slow peritoneal clearance of some drugs
- 1984:** Feasibility of intermittent large volume IP therapy
- 1996:** First report of a survival benefit for IP vs intravenous (IV) chemotherapy in advanced ovarian cancer

Intraperitoneal Chemotherapy: GOG 172

Ovarian cancer
Optimal (<1 cm)
Stage III

Stratify:
Gross residual
Planned 2nd look

R
A
N
D
O
M
I
Z
E

Paclitaxel 135 mg/m²/24h
Cisplatin 75 mg/m²
q 21 days x 6

Paclitaxel 135 mg/m²/24h
Cisplatin 100 mg/m² IP D2
Paclitaxel 60 mg/m² IP D8
q 21 days x 6

GOG 172: Efficacy Data

	Regimen 1 <u>Intravenous</u>	Regimen 2 <u>Intraperitoneal</u>
Progression-free survival	18.3 months	23.8 months
Overall survival	49.7 months	65.6 months

GOG 172: Hematologic Toxicities

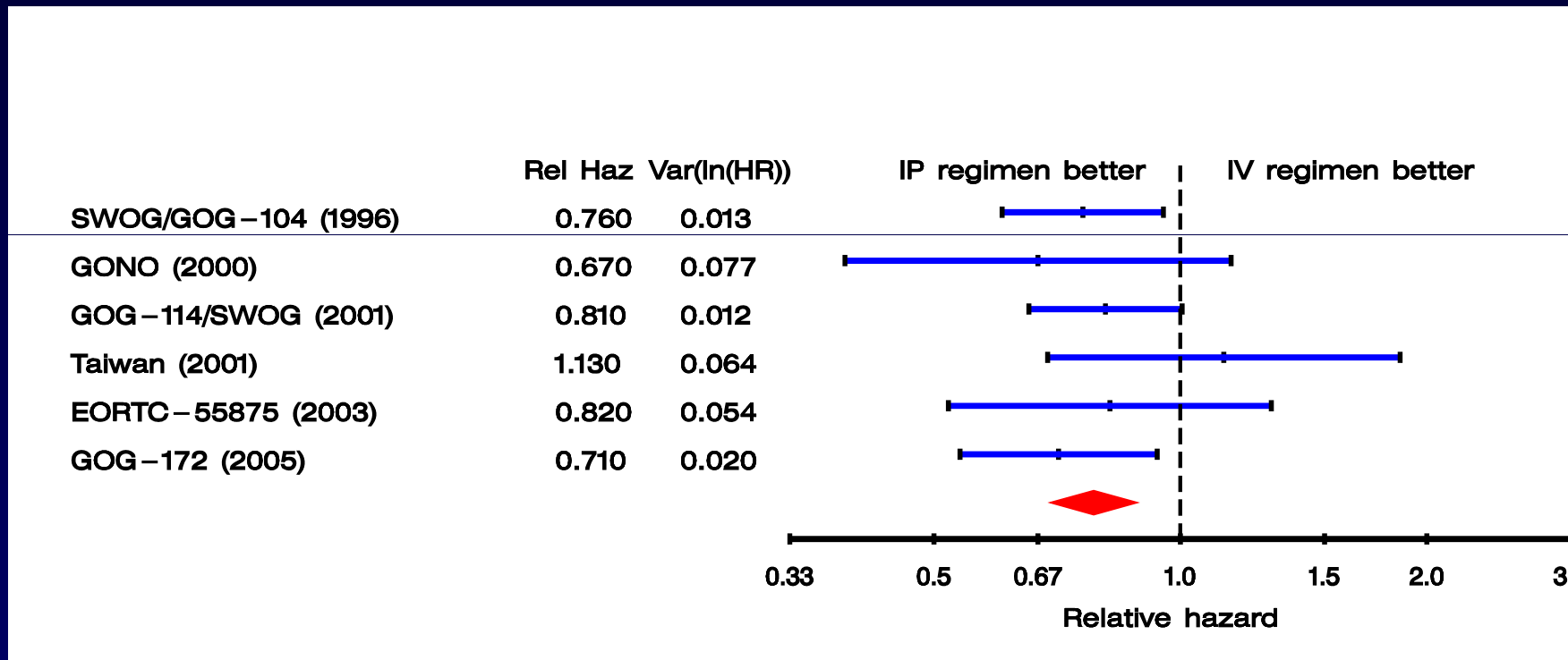
	IV, %	IP, %	<i>P</i>
Leukopenia grade 3/4	64	76	<.001
Infection grade 3/4	6	16	.001
Platelet count <25,000/mm ³ grade 3/4	4	12	.002

Cycles of IP Chemotherapy Given Successfully

Number of IP cycles completed (n = 205)

No of IP Cycles	No of Patients	% of Patients
0	16	8
1	38	19
2	30	15
3	14	7
4	10	5
5	11	5
Failed: <6 cycles	119	58
Success: 6 cycles	86	42
Total	205	100

Treatment Hazard Ratios for Death Intraperitoneal vs Intravenous Therapy



I^2 heterogeneity (5 d.f.) = 3.1, $P = .68$

Hazard ratio is not reported for the GONO study but it is calculated from the available data reported.

Hazard ratio is not reported for the Greek study.

12/29/05

NCI Clinical Announcement

NATIONAL
CANCER
INSTITUTE

The logo of the National Cancer Institute, featuring the words "NATIONAL", "CANCER", and "INSTITUTE" stacked vertically in a serif font, with a horizontal line below the word "INSTITUTE". The logo is set against a red rectangular background.

Intraperitoneal chemotherapy for ovarian cancer

- The purpose of a clinical announcement is to alert clinicians and patients about major advances in treatment
- A clinical announcement on IP in January 2006

“IP chemotherapy should be considered for optimally debulked patients”

Previous NCI Clinical Announcements

- **Adjuvant therapy for node-negative breast cancer, 1988**
- **Levamisole and 5FU for Dukes C colon cancer, 1989**
- **Adjuvant therapy for rectal cancer, 1991**
- **Update on tamoxifen as adjuvant for breast cancer, 1995**
- **Chemoradiation for cervical cancer, 1999**

2000-2008 Phase III Strategies

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 - MITO-2

Weekly Paclitaxel

- 3 weekly paclitaxel therapy is established
- Weekly paclitaxel considered potentially because:
 - More effective in breast cancer
 - Antiangiogenetic effect
 - Active in second-line in several phase II studies in ovarian cancer
 - Less toxic
- → The JGOG study

JGOG Study Design

Ovarian epithelial, primary,
peritoneal, or
fallopian tube cancer
FIGO stage II-IV

Randomization stratified by

- *Residual disease*
- *FIGO stage*
- *Histology*

Conventional TC (c-TC)

Paclitaxel 180 mg/m² Day 1
Carboplatin AUC 6.0 Day 1
every 21 days for 6-9 cycles

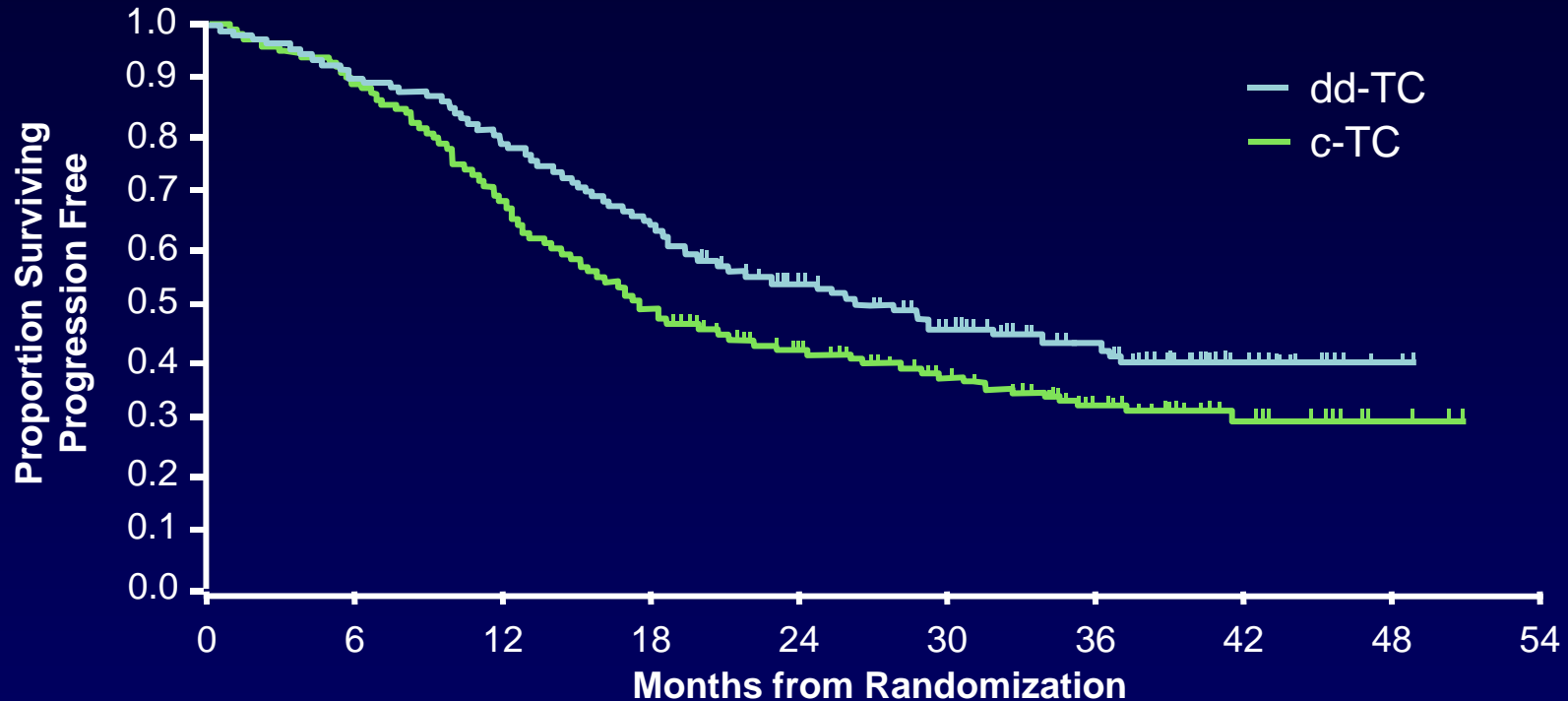
Dose-dense weekly TC (dd-TC)

Paclitaxel 80 mg/m² Days 1, 8, 15
Carboplatin AUC 6.0 Day 1
every 21 days for 6-9 cycles

JGOG Study: Responses

Measurable	Patients (%)	
	c-TC (n = 135)	dd-TC (n = 147)
Objective response	53	56
Complete response	16	20
Partial response	38	36
NC	31	29
PD	7	3
NE	9	12

JGOG Study: PFS



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

Isonishi S, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 5506.

First-Line Weekly Carboplatin and Paclitaxel vs Every 3 Weeks Carboplatin/Paclitaxel in Patients with Ovarian Cancer: The MITO-7 Trial

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

RANDOM

**Carboplatin AUC 6
Paclitaxel 175 mg/mq**

day 1 - every 21days

**Carboplatin AUC 2
Paclitaxel 60 mg/mq**

day 1,8, 15 - every 21 days

2000-2008 Phase III Strategies

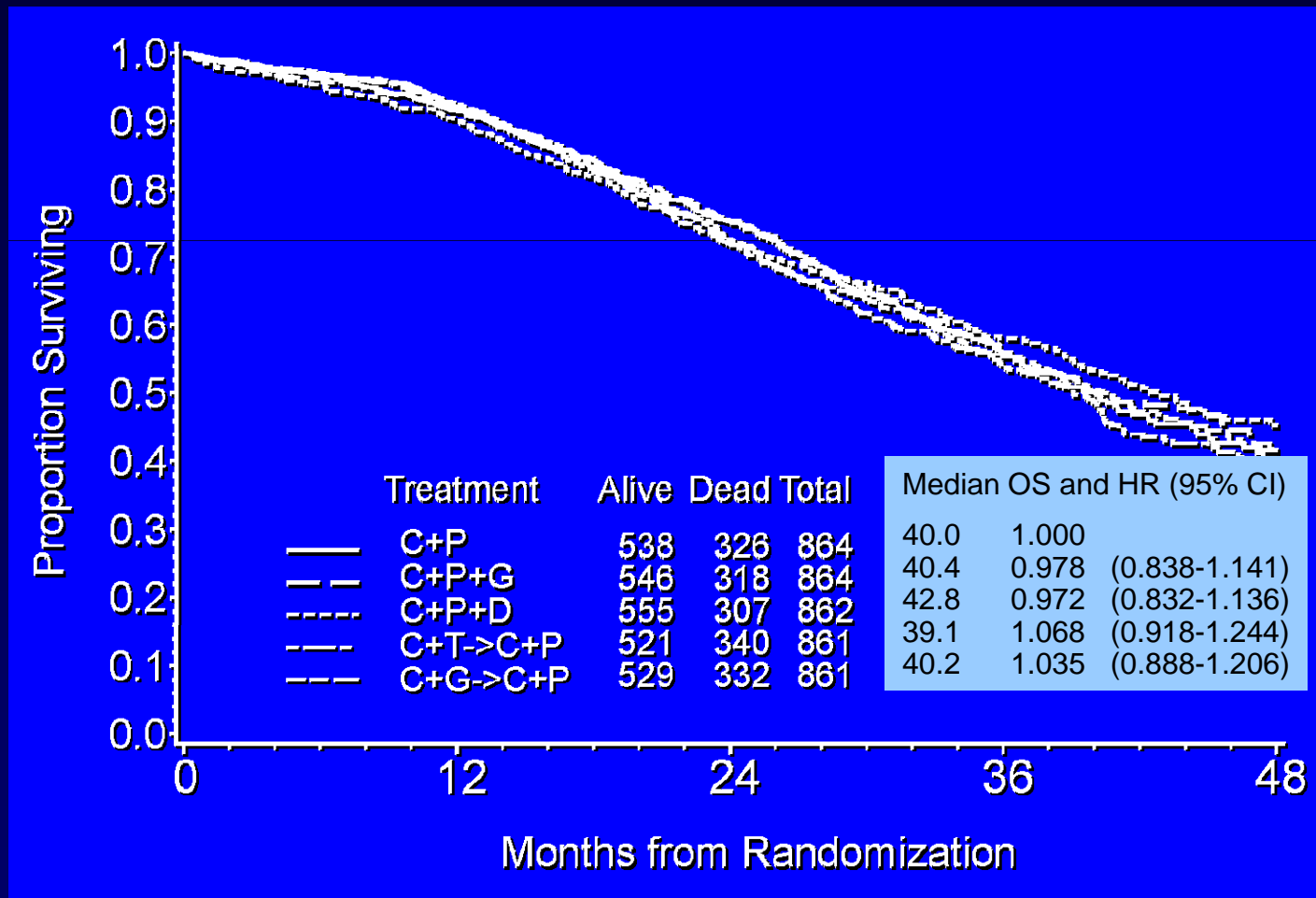
- Intraperitoneal (IP) chemotherapy
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- **Add new drugs**
 - GOG 182 – ICON5
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GOG0182-ICON 5

R A N D O M	I	Carboplatin AUC 6 (d1) Paclitaxel 175 mg/m ² (d1)	x8
	II	Carboplatin AUC 5 (d1) Paclitaxel 175 mg/m ² (d1) Gemcitabine 800 mg/m ² (d1,8)	x8
	III	Carboplatin AUC 5 (d1) Paclitaxel 175 mg/m ² (d1) Doxil 30 mg/m ² (d1, every other cycle)	x8
	IV	Carboplatin AUC 5 (d3) Topotecan 1.25 mg/m ² (d1-3)	x4
	V	Carboplatin AUC 6 (d8) Gemcitabine 1 g/m ² (d1,8)	x4

Carboplatin AUC 6 (d1) Paclitaxel 175 mg/m ² (d1)	x4
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GOG0182-ICON5: Overall Survival



2000-2008 Phase III Strategies

- **Intraperitoneal (IP) chemotherapy**
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 - MITO-2

Carboplatin plus Paclitaxel versus Carboplatin plus Pegylated Liposomal Doxorubicin (PLD) in Patients with Advanced Ovarian Cancer: Activity and Safety Results of the MITO-2 Randomized Multicenter Trial



S. Pignata¹, G. Scambia², A. Savarese³, R. Sorio⁴, E. Breda⁵,
G. Ferrandina², V. Gebbia⁶, P. Musso⁷, C. Gallo⁸, F. Perrone⁹

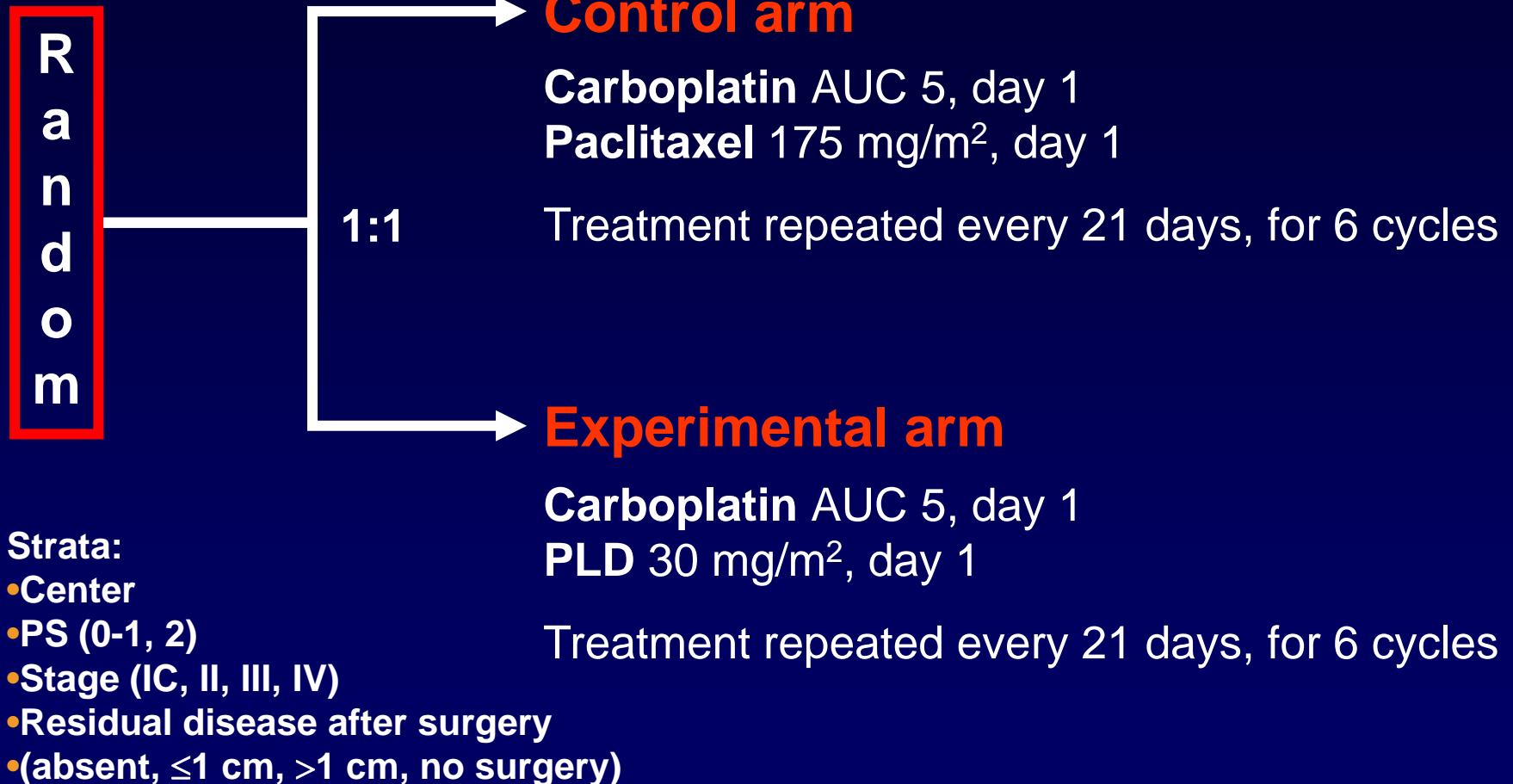
¹Istituto Nazionale Tumori, Napoli; ²Università Cattolica del Sacro Cuore, Roma; ³Istituto Regina Elena, Roma; ⁴CRO, Aviano; ⁵Ospedale Fatebenefratelli, Isola Tiberina, Roma;

⁶Casa di Cura La Maddalena, Università di Palermo; ⁷Ospedale Oncologico M.Ascoli A.R.N.A.S., Palermo; ⁸Seconda Università di Napoli; ⁹Istituto Nazionale Tumori di Napoli, Italy.

Study Objective

MITO-2 is a randomized phase III study testing whether carboplatin plus PLD is more effective than carboplatin plus paclitaxel as first-line treatment of patients with advanced ovarian cancer

Study Design



Study Endpoints

Primary endpoint

- Progression-free survival (PFS)

Secondary endpoints

- Overall survival (OS)
- Objective response rate (RECIST)
- Toxicity (NCI – CTC v2.0)
- Quality of Life (EORTC QLQ C30)

Sample Size

- **2-tailed α : 0.05**
 - **Power: 80%**
 - **Hazard Ratio: 0.80**
 - **Median PFS in control arm: 18 months**
 - **Median PFS in experimental arm: 22.5 months**
- **632 events (progressions) needed**
- **820 patients planned**

Study Conduction

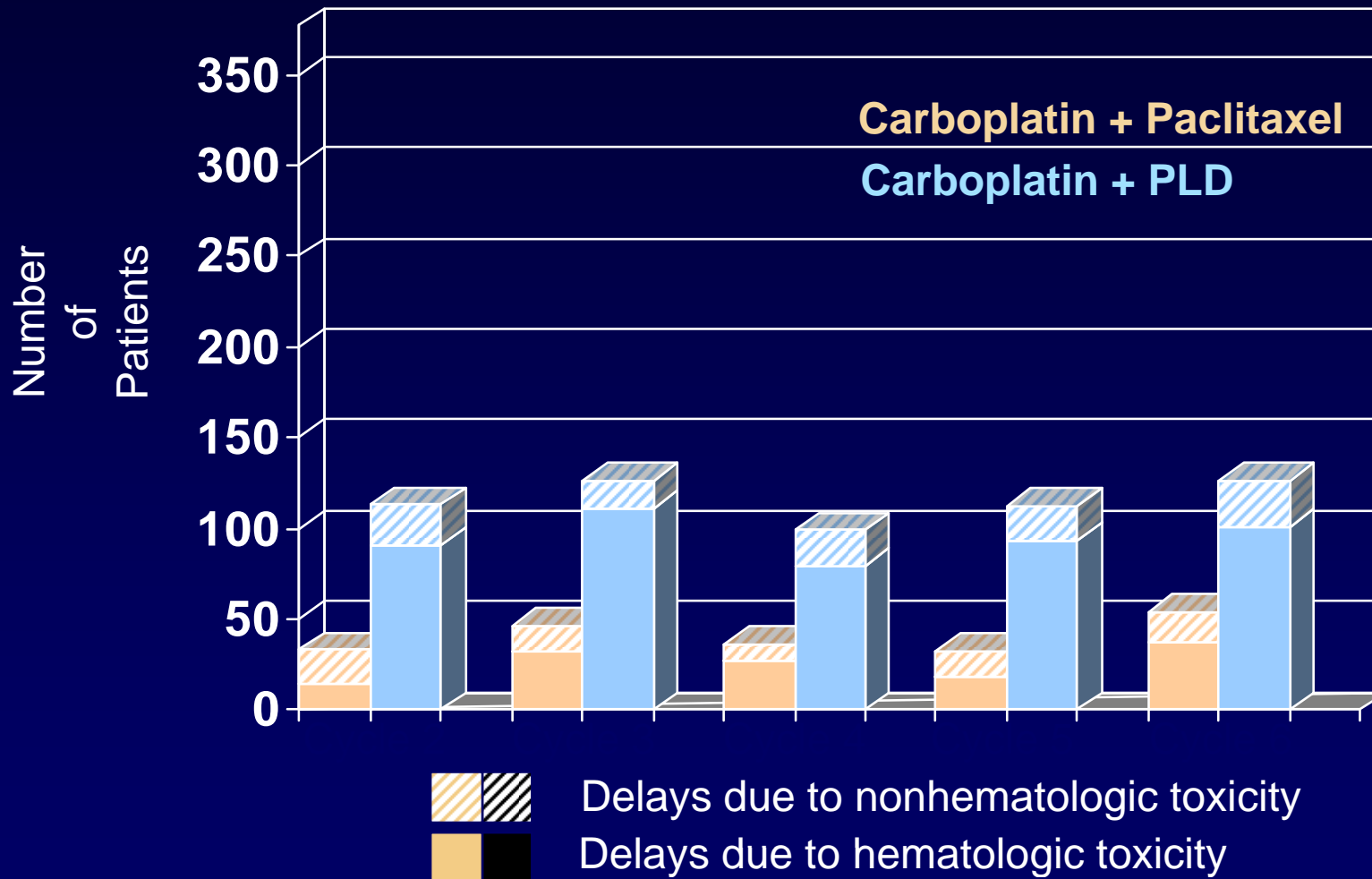
- **First patient enrolled: January 17, 2003**
- **Last patient enrolled: November 9, 2007**
- **42 active Institutions (41 Italy, 1 Portugal)**
- **820 randomized patients (809 Italy, 11 Portugal)**
- **Preplanned early safety analysis:**
 - **First 50 patients receiving carboplatin + PLD¹**
- **Preplanned interim activity analysis:**
 - **First 50 patients eligible for RECIST assigned to carboplatin + PLD²**

1. Pignata S, et al. *BMC Cancer*. 2006;6:202. 2. Pignata S, et al. *Oncology*. 2009;76(1):49-54.

Treatment Compliance

	Carbo + Paclitaxel (n = 410)	Carbo + PLD (n = 410)
Pending information	29 (7%)	27 (7%)
Did not start treatment	4 (1%)	6 (1%)
Number of cycles received*		
1	10 (3%)	11 (3%)
2	13 (3%)	19 (5%)
3	8 (2%)	13 (4%)
4	6 (2%)	11 (3%)
5	10 (3%)	14 (4%)
6	330 (88%)	309 (82%)

Treatment Compliance: Delays



Pignata S, et al. *Oncology*. 2009;76(1):49-54.

Treatment Compliance: Delays



- 60% of patients with at least 1 cycle delayed
- 65% of cycles given on time at day 21



Delays due to nonhematologic toxicity

Delays due to hematologic toxicity

Toxicity (1)

	Any Grade			Severe (G \geq 3)		
	C+P	C+PLD	P*	C+P	C+PLD	P*
Toxic deaths				0.8%	0.5%	1
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
Bleeding	0.3%	1%	.37	-	1%	.24

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

*Chi square or Fisher exact test as appropriate

Toxicity (2)

	Any Grade			Severe (G \geq 3)		
	C+P	C+PLD	P*	C+P	C+PLD	P [^]
Allergy	6%	5%	.60	2%	2%	.86
Heart	2%	4%	.26	0.3%	2%	.06
Fatigue	44%	43%	.86	3%	3%	.94
Constipation	32%	32%	.99	1%	1%	.73
Nausea	47%	51%	.21	2%	2%	.95
Vomiting	29%	30%	.83	2%	3%	.42
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. *Oncology*. 2009;76(1):49-54.

Activity Analysis: Flow of Patients

**Carbo + Paclitaxel
(n = 410)**

**Carbo + PLD
(n = 410)**



Analysis performed according to “*intention to treat*” principle

Objective Response—RECIST Women with Target Lesions

	Carbo + Paclitaxel (n=156)	Carbo + 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

Activity

Women Not Eligible for RECIST

	Carbo + Paclitaxel	Carbo + PLD	<i>P</i> (χ^2)
Nontarget lesions only			
Complete response (CR)	27 / 83 (33%)	29 / 99 (29%)	.64*
No CR / No PD	46 / 83 (55%)	48 / 99 (48%)	
Progressive disease	2 / 83 (2%)	4 / 99 (4%)	
Not evaluated	8 / 83 (10%)	18 / 99 (18%)	
Elevated Ca125 only			
Ca125 normalized	73 / 88 (83%)	69 / 80 (86%)	.56**

* Complete response vs not

** Ca125 normalized vs not

Pignata S, et al. *Oncology*. 2009;76(1):49-54.

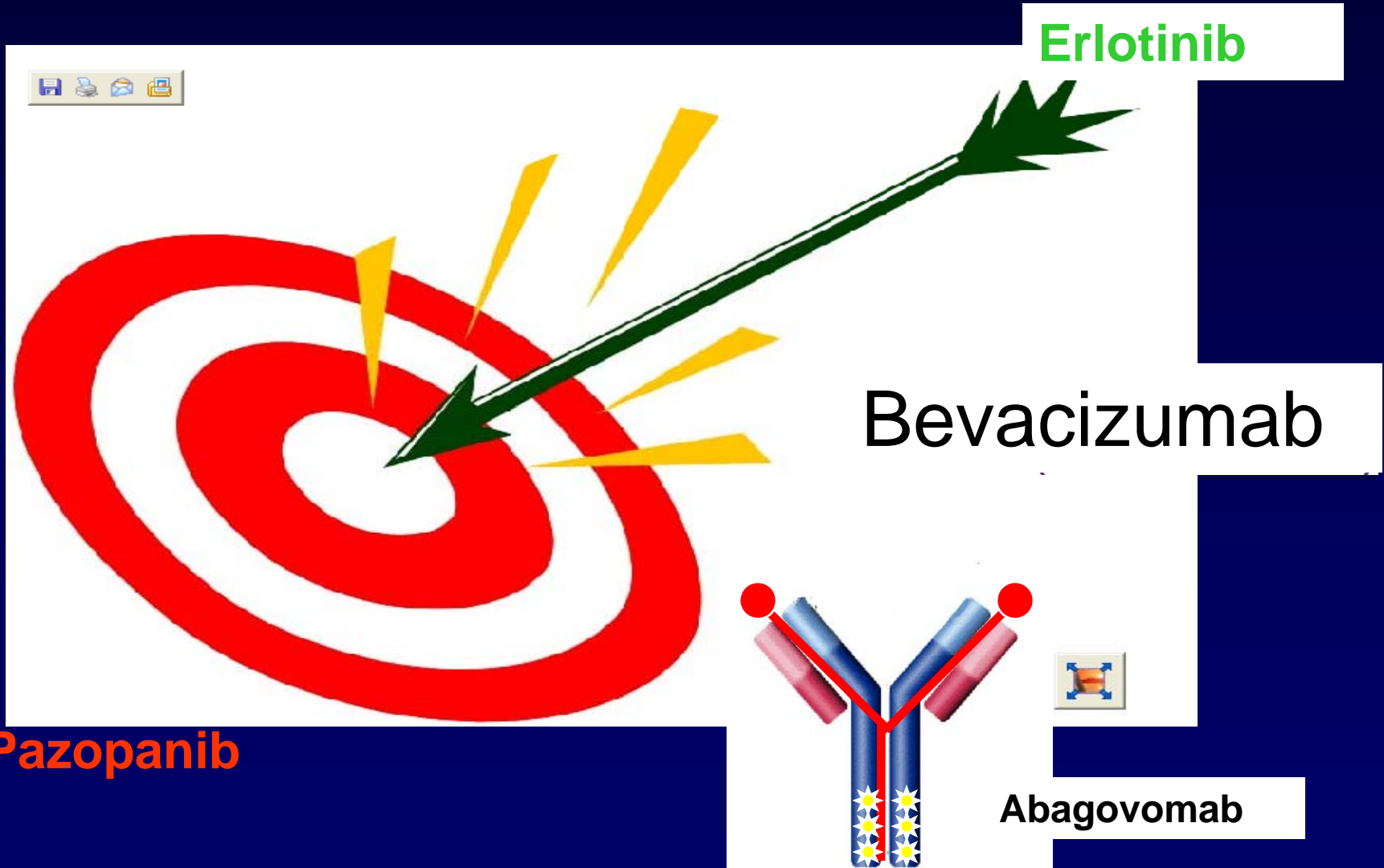
MITO2 Preliminary Conclusions (1)

- **Toxicity profile of carboplatin plus PLD as first-line treatment of advanced ovarian cancer is markedly different from carboplatin plus paclitaxel**
- **Carboplatin plus PLD is associated with:**
 - Higher incidence of anemia and thrombocytopenia (rarely requiring transfusions)
 - Higher incidence of stomatitis and cutaneous toxicity (that are rarely severe)
 - Lower incidence of hair loss and neurotoxicity

MITO2 Preliminary Conclusions (2)

- **There was no statistically significant difference in response rate between carboplatin plus PLD and carboplatin plus paclitaxel**
- **Final analysis for the primary endpoint (PFS) will be performed as soon as the required number of events will be reached**

Waiting for Biological Agents



Conclusions

- **Carboplatin-paclitaxel is the standard**
- **Need for improvement after more than 10 years!! (efficacy/safety)**
- **Modulation of paclitaxel activity**
- **Substitution of paclitaxel with PLD**
- **Incorporate biological therapies in the chemotherapy scenario**