

# Debate Question

**Do you believe that the management of a partially platinum-sensitive relapse (6-12 months) of epithelial ovarian cancer should involve platinum-based combination chemotherapy?**

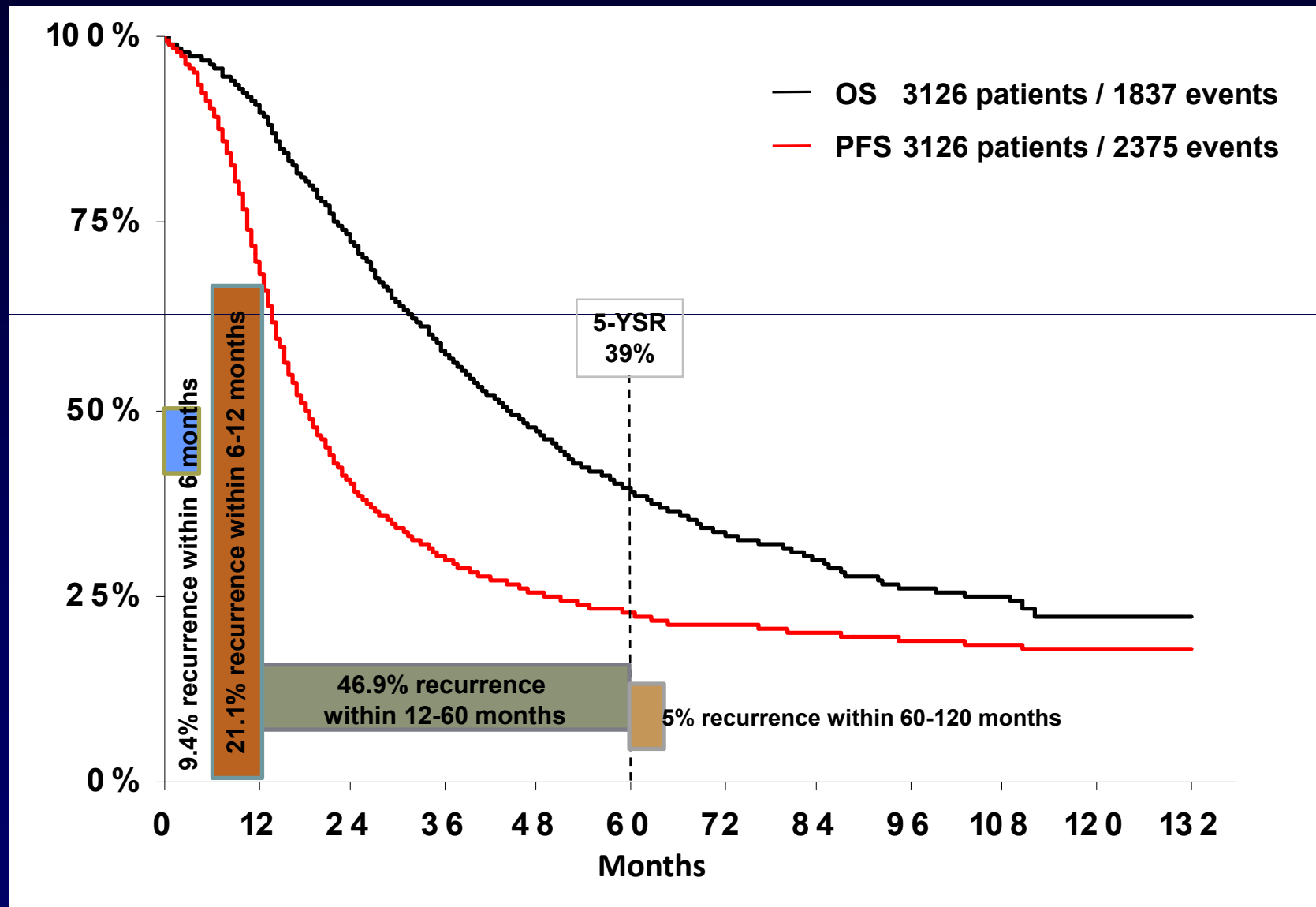
- **Yes**
- **No**
- **Need more information**

# Management of a Partially Platinum-Sensitive Relapse (6-12 Months) of Ovarian Cancer Should Involve Platinum-Based Combination Chemotherapy

## Pro

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## Overall and Progression-Free Survival in Advanced Ovarian Cancer FIGO IIB-IV (All Patients) An Individual Patients Metaanalysis of AGO-OVAR 3, AGO-OVAR 5, and AGO-OVAR 7



# Clinical Situation

- The patient had most likely had primary treatment with carboplatin and paclitaxel
- Thus, she has a 20% probability of suffering from delayed neurotoxicity
- Her hair started recently to grow back again

# Paclitaxel Plus Platinum-Based Chemotherapy Versus Conventional Platinum-Based Chemotherapy In Women With Relapsed Ovarian Cancer: The ICON4/AGO-OVAR-2.2 Trial

## Design

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- 802 patients
- Relapsed OC >6/ >12 months after platinum
- 1 prior pt regimen with platinum (Italy) or platinum-paclitaxel (AGO OVAR)
- At least 1 prior pt.-regimen (UK)

Study arm

n = 392

Paclitaxel 175-185 mg/m<sup>2</sup> (3h)  
+  
Carboplatin AUC 5-6  
or Cisplatin (10%)

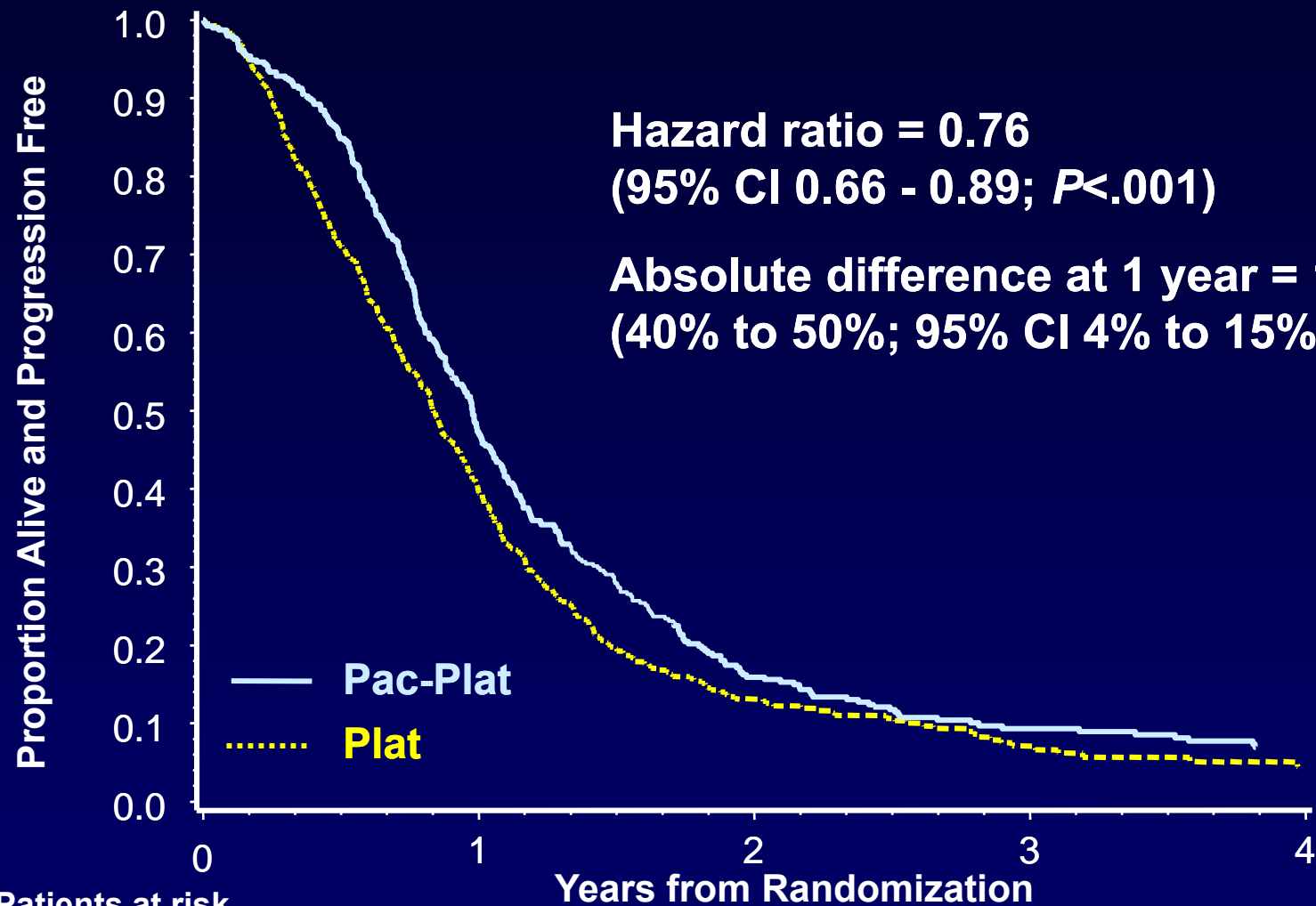
Standard

n = 410

Platin without paclitaxel

- Carboplatin mono (71%)
- Cisplatin mono (2%)
- other platin regimens (27%)

# Progression-Free Survival (PFS)



Patients at risk

Pac-Plat

392

179

52

25

17

Plat

410

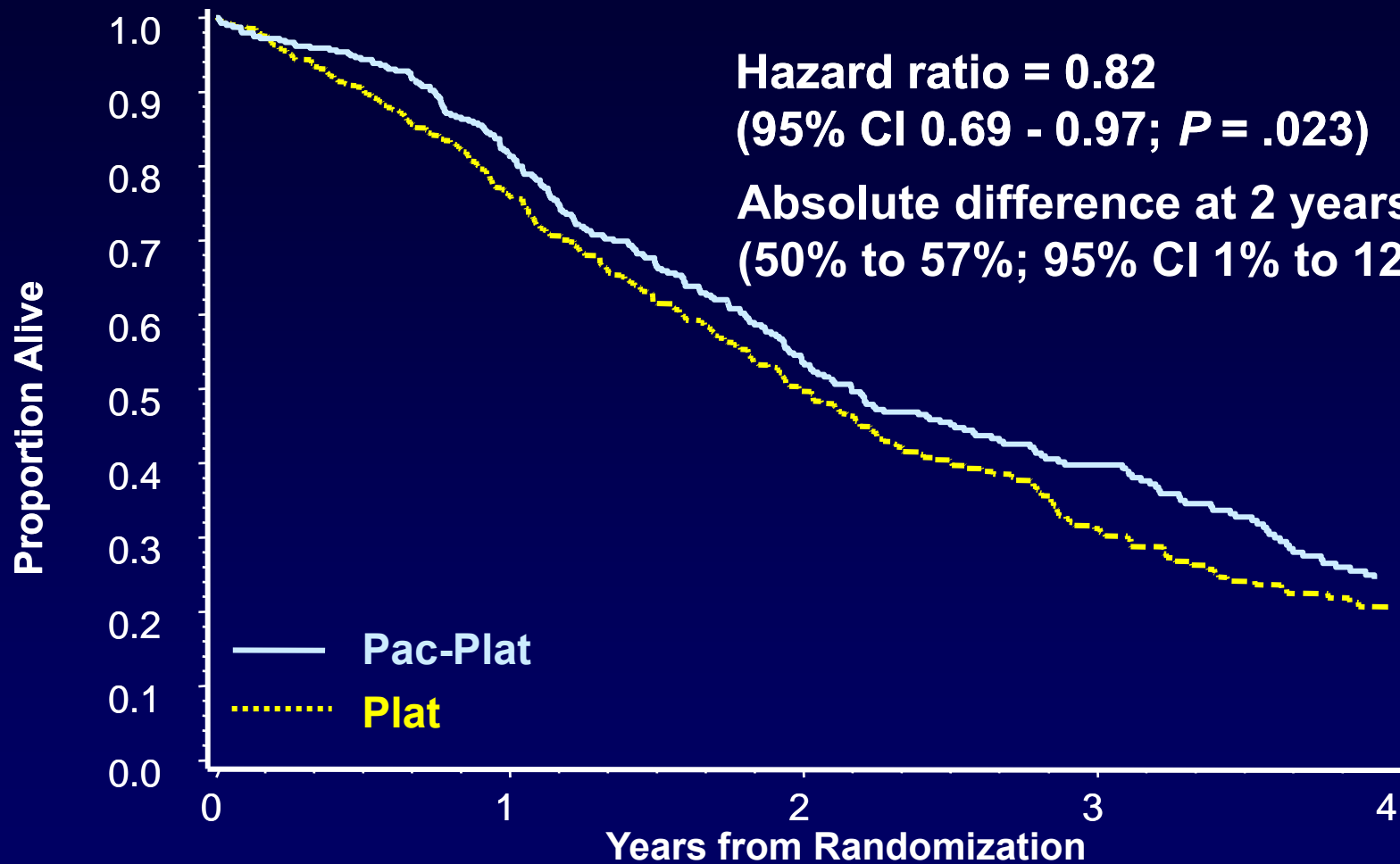
157

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# Overall Survival (OS)



## Patients at risk

Pac-Plat	392	306	167	96	43
Plat	410	295	150	68	33

Parmar MK, et al. *Lancet*. 2003;361(9375):2099-2106.

# Moderate or Severe Toxicities

Toxic Effect	Paclitaxel + Platinum (n = 392)	Conventional Platinum Therapy (n = 410)
<b>Neurologic</b>	<b>76 (20%)</b>	<b>4 (1%)</b>
Hematologic	111 (29%)	182 (46%)
Alopecia	322 (86%)	95 (25%)
Nausea + vomiting	131 (35%)	153 (40%)

# GCIIG Trial Gem/Carbo vs Carbo AGO OVAR – NCIC CTG – EORTC GCG Design

- Recurrent ovarian cancer with at least evaluable disease
- 6+ months after platinum
- Strata:
  - Platinum-free interval (6-12, >12 months)
  - First-line therapy (platinum +/- paclitaxel)
  - Measurable disease vs evaluable disease

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Gemcitabine 1000 mg/m<sup>2</sup> d 1+8  
Carboplatin AUC 4 d 1  
q 21 x 6 (-10)

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

# GCIG Trial Gem/Carbo vs Carbo AGO OVAR – NCIC CTG – EORTC GCG

## Hematologic Toxicity (Worst of Courses/Patient)

	Gem/Carbo	Carbo	P Value
Grade 3+4 (% of patients)	78.3	24.7	<.001
Anemia	27.4	8.0	<.001
Thrombocytopenia	34.9	11.5	<.001
Neutropenia	70.3	12.1	<.001
Febrile neutropenia	1.1	0.0	NS
Infections	0.6	0.6	NS
G9M)-CSF	23.6	10.1	<.001
Parenteral antibiotics	8.4	5.1	NS
RBC	27.0	6.7	<.001

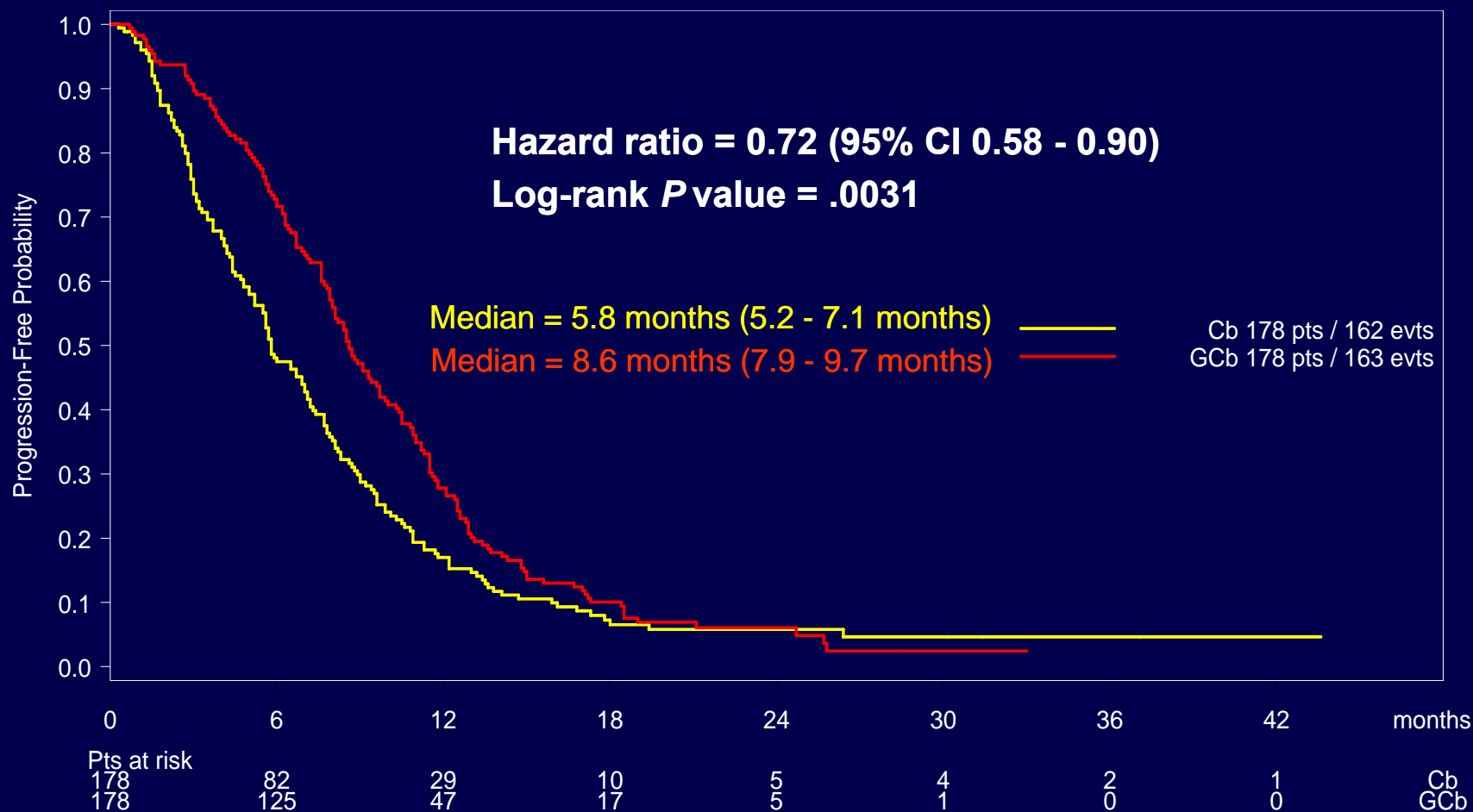
# GCIG Trial Gem/Carbo vs Carbo AGO OVAR – NCIC CTG – EORTC GCG

## Nonhematologic Toxicity (Worst of Courses/Patient)

	Gem/Carbo	Carbo	P Value
<b>Grade 3 + 4 (% of patients)</b>	<b>12.6</b>	<b>9.2</b>	<b>NS</b>
Alopecia (grade 2)	14.3	2.3	<.001
Emesis	2.9	1.7	NS
Nausea	4.0	1.7	NS
Diarrhea	1.7	0.0	NS
Sens. Neurotoxicity	1.1	1.7	NS
Sens. Neurotoxicity (grade 2)	4.0	3.4	NS
Stomatitis	0.6	0.0	NS
Fatigue	2.3	1.7	NS
Hypersensitivity	2.3	2.9	NS

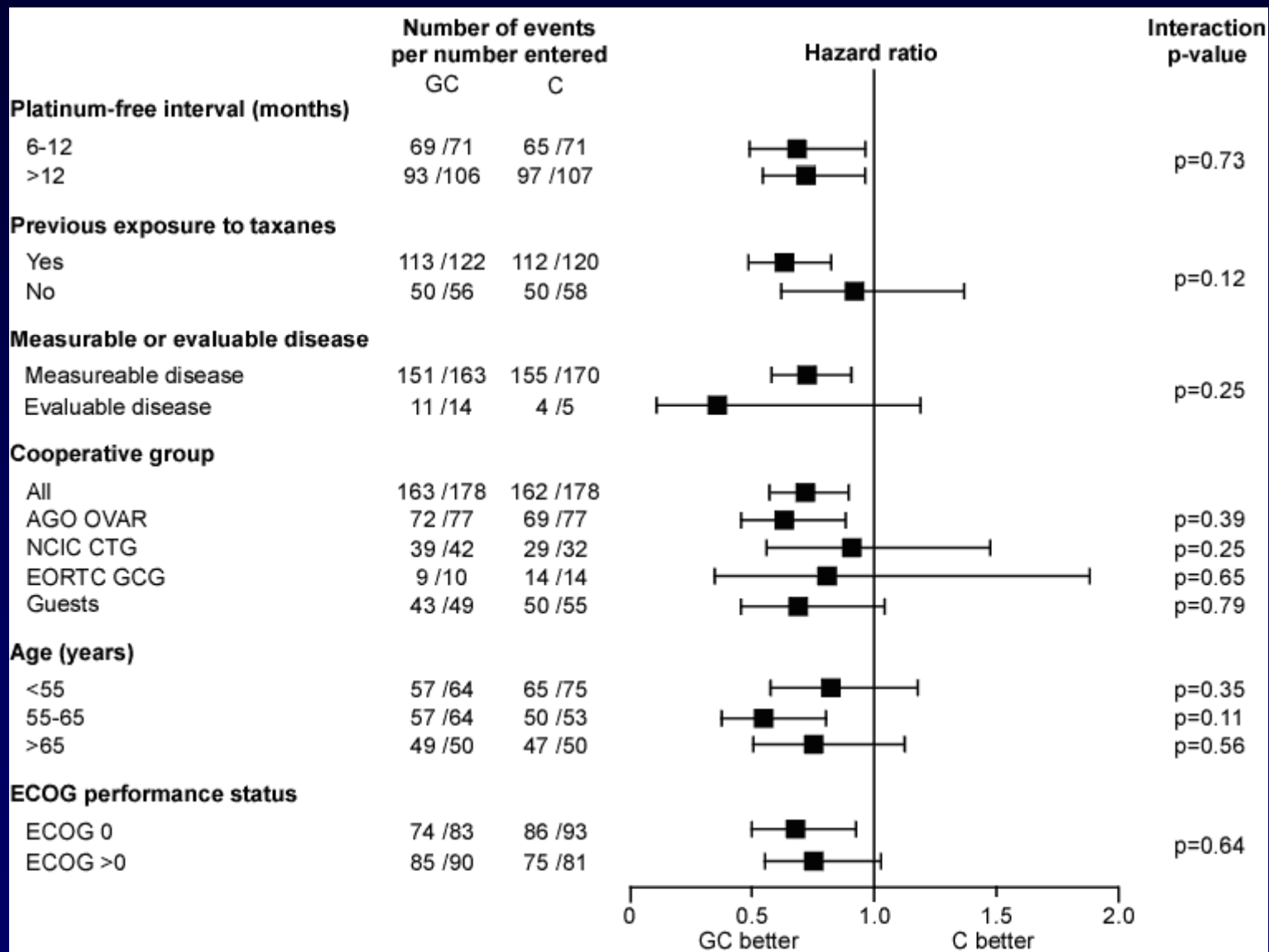
# GCIIG Trial Gem/Carbo vs Carbo AGO OVAR – NCIC CTG – EORTC GCG

## Progression-Free Survival by Therapy



Pfisterer J, et al. *J Clin Oncol.* 2006;24(29):4699-4707.

# GCI Trial Gem/Carbo vs Carbo Exploratory Subgroup Analysis



# Platinum-Based Combination Therapies in Platinum-Sensitive Recurrent Ovarian Cancer

- **Paclitaxel + Carboplatin**

- Effective (PFS, OS)
- Schedule: d1 q 3 w
- **Neurotoxicity**
- **Alopecia 86%**
- QoL: No worsening

- **Gemcitabine + Carboplatin**

- Effective (PFS)
- **Schedule: d1 + 8 q 3 w**
- **Hematologic toxicity**
- Alopecia 15%
- QoL: No worsening

# **GINECO Phase II Study PLD + Carboplatin**

- **105 patients with platinum-sensitive recurrent ovarian cancer**
- **Schedule (1 day every 4 weeks)**
- **PLD 30 mg/m<sup>2</sup>, 1 hour iv**
- **Carboplatin, AUC 5 mg/mL<sup>-1</sup>/min, 30 min iv**

# GINECO Phase II Study PLD + Carboplatin

## Efficacy

Variable	
Response	%
Overall	63
Complete response	38
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Progression-free survival	Median, months
Overall	9.4
TFI $\geq$ 12 months	11.4
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Survival	32

# CALYPSO Study Schema

International, Intergroup, Open-Label, Randomized Phase III Study

Ovarian cancer in late relapse (>6 months) after first-line or second-line platinum-based therapy (previous taxane required)

## Stratification:

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

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Experimental arm: CD

**PLD 30 mg/m<sup>2</sup> IV d 1**

**Carboplatin AUC 5 d 1**

**Q 28 days x 6 courses\***

Control arm: CP

**Paclitaxel 175 mg/m<sup>2</sup> IV d 1**

**Carboplatin AUC 5 d 1**

**Q 21 days x 6 courses**

\*Or progression in patients with SD or PR

# Endpoints. Statistical Discussions<sup>1</sup>

## Primary endpoint

- Progression-free survival (PFS)

## Statistical considerations

- Two-arm, parallel, NONINFERIORITY study design
- Statistical assumptions based on PFS from ICON4/AGO-OVAR 2.2 trial<sup>2</sup>
- Declare noninferior if HR one-side 95% CI  $< 1.23$  (CD:CP) for PFS
- Power of 90% and one-sided confidence level of 95%
- Number of events required: 745

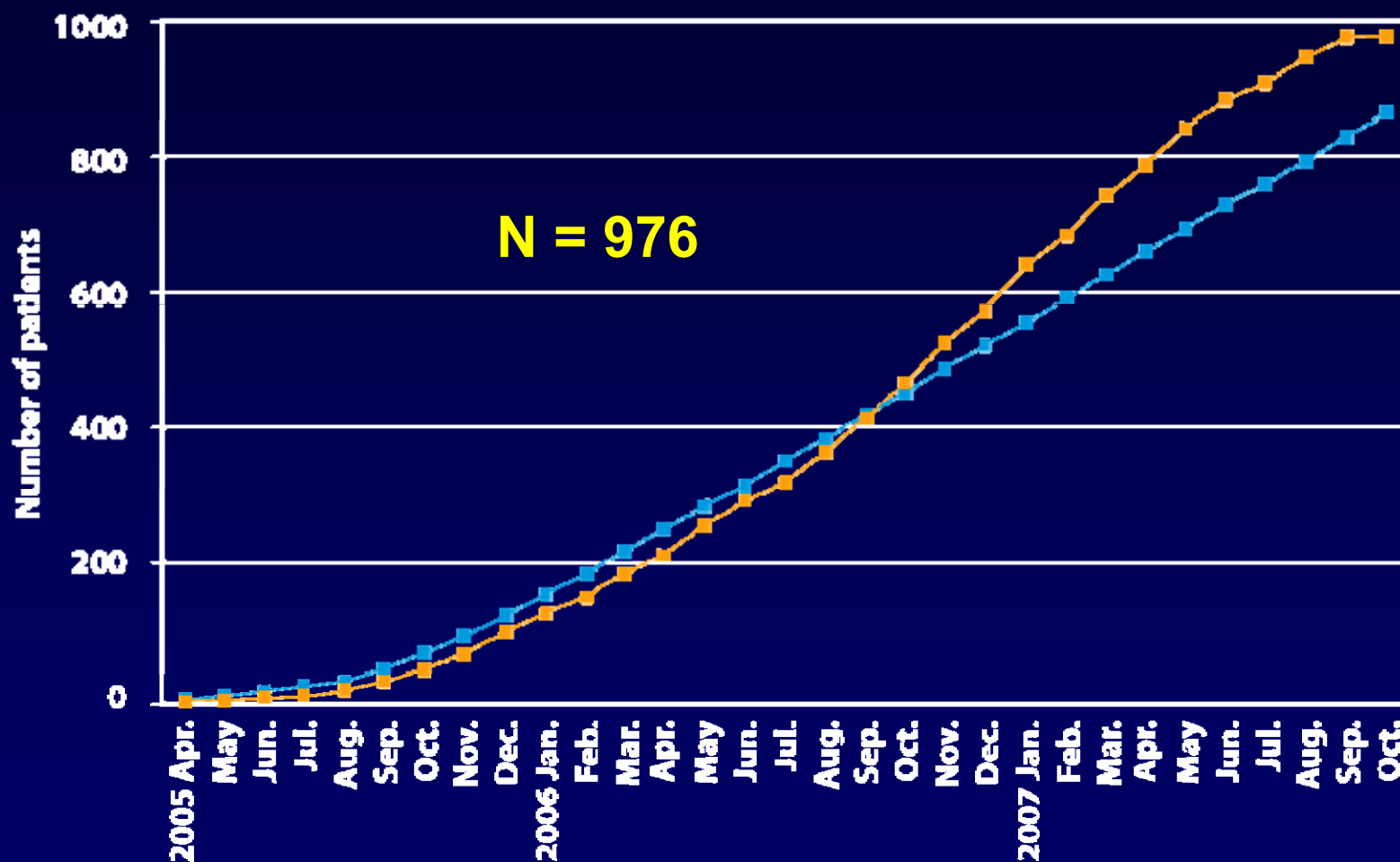
1. Pujane-Lauraine E, et al. *J Clin Oncol*. 2009;27(15S): Abstract LBA5509. 2. Parmar MK, et al. *Lancet*. 2003;361(9375):2099-2106.

# Endpoints

## Secondary endpoints

- Qualitative and quantitative toxicities
- Quality of life (EORTC QLQ-C-30 version 3.0 and OV-28 questionnaire version 1.0)
- Overall survival

# Accrual



Pujade-Lauraine E, et al. *J Clin Oncol.* 2009;27(18S): Abstract LBA5509.

# Baseline Characteristics (1)

Characteristic	CD (n = 466)	CP (n = 508)
	Number of Patients (%)	
Age, median	60.5	61.0
ECOG performance status*		
0	286 (61)	317 (62)
1	159 (34)	164 (32)
2	13 (3)	15 (3)
Primary site of disease		
Ovarian	415 (89)	451 (89)
Papillary/serous histology	334 (72)	366 (72)
Initial FIGO stage*		
I/II	52 (11)	59 (12)
III/IV	401 (86)	427 (84)
Number of previous lines		
One	408 (88)	421 (83)
Two	58 (12)	87 (17)

\* Missing values to attain 100%.

Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

## Baseline Characteristics (2)

Characteristic	CD (n = 466)	CP (n = 508)
	Number of Patients (%)	
Prior taxane	462 (99)	500 (99)
Interval since prior therapy, median		
6-12 months	162 (35)	182 (36)
> 12 months	304 (65)	326 (64)
Measurable disease		
Yes	281 (60)	321 (63)
No	185 (39)	188 (37)
Tumor size		
< 5 cm	377 (81)	419 (82)
≥ 5 cm	89 (19)	90 (18)
Number of sites		
1	217 (47)	245 (48)
>1	249 (53)	264 (52)

# Treatment Exposure

	CD (n = 465)**	CP (n = 501)**
<b>Total treatment duration, median week*</b>	<b>21</b>	<b>16</b>
Relative dose intensity %	Carbo: 99 PLD: 99	Carbo: 99 Paclitaxel: 98
<b>Patients with ≥6 cycles, n (%)*</b>	<b>395 (85)</b>	<b>392 (78)</b>
Patients with ≥9 cycles, n (%)	36 (8)	36 (7)

\*  $P < .001$ ; \*\* Patients receiving at least one cycle

# Hematologic Toxicity

Toxicity	CD	CP	P Value
	(n = 464)	(n = 500)	
	Number of Patients (%)		
<b>Neutropenia, grade 3</b>	<b>144 (31)</b>	<b>121 (24)</b>	<b>&lt;.01</b>
<b>grade 4</b>	<b>20 (4)</b>	<b>108 (22)</b>	
Febrile neutropenia, grade 3-4	10 (2)	21 (4)	NS
Infection, grade 3-4	11 (3)	14 (3)	NS
<b>Thrombocytopenia, grade 3-4</b>	<b>73 (16)</b>	<b>31 (6)</b>	<b>&lt;.01</b>
Bleeding, grade 3-4	3 (0.6)	0 (0)	NS
Anemia, grade 3-4	37 (8)	27 (5)	NS

NS = not significant

# Selected Nonhematologic Toxicities During Treatment

	CD (n = 466)		CP (n = 501)	
	Grade 2	Grade 3/4	Grade 2	Grade 3/4
<b>Nausea/vomiting*</b>	<b>31%</b>	4%	20%	4%
Constipation	19%	2%	20%	2%
Diarrhea	4%	2%	6%	2%
<b>Arthralgia/myalgia*</b>	4%	0%	<b>18%</b>	1%
<b>Hand-foot syndrome*</b>	<b>11%</b>	2%	2%	0%
<b>Mucositis*</b>	<b>13%</b>	2%	6%	1%
Fatigue	31%	7%	34%	7%
Cardiac disorders	2%	1%	3%	1%

\* $P < .001$

# Selected Nonhematologic Toxicities During Treatment

## Alopecia

	CD (n = 466)	CP (n = 501)
<b>Alopecia grade 2*</b>	<b>7%</b>	<b>84%</b>

*P* < .001

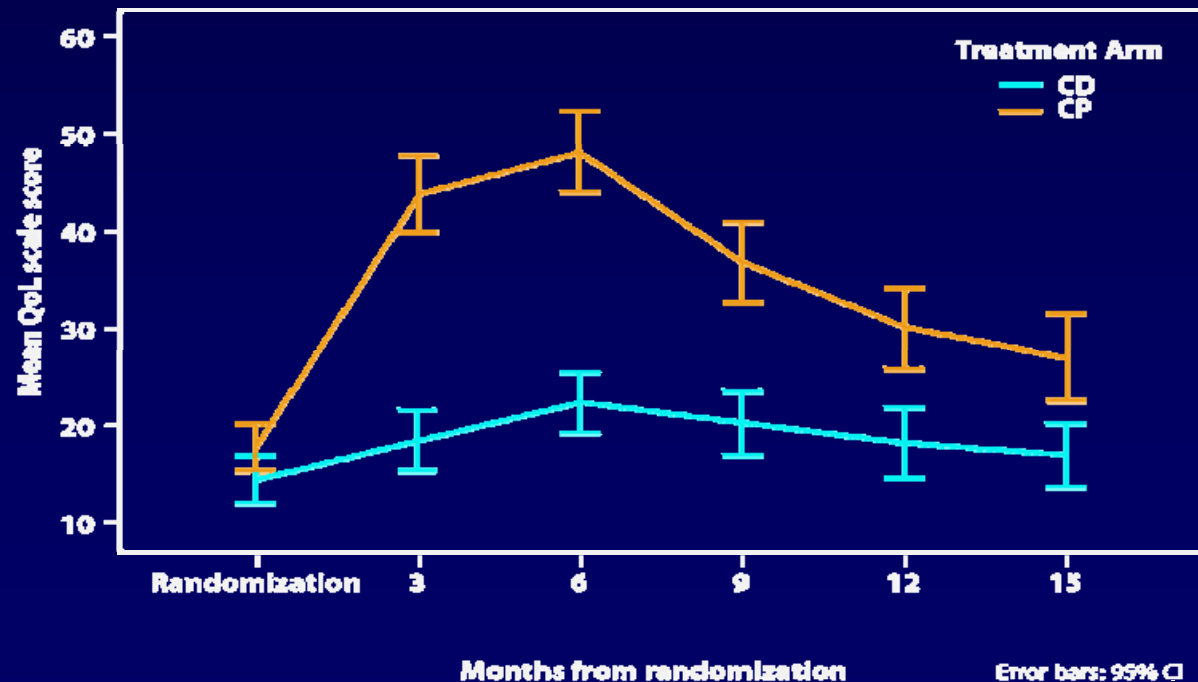
# Long-Lasting Toxicity

	CD (n = 466)		CP (n = 501)	
	Grade 2	Grade 3/5	Grade 2	Grade 3/5
<b>Neuropathy*</b>	4%	1%	<b>24%</b>	<b>4%</b>

\*  $P < .001$

EORTC OV28 – QoL Peripheral Neuropathy

Neuropathy score over time



# Early Treatment Discontinuation

Reason	CD (n = 466)	CP (n = 501)
<b>Toxicity*</b>	<b>27 (6)</b>	<b>73 (15)</b>
Patient/investigator choice	16 (3)	14 (3)
Progressive disease	26 (6)	22 (4)
Intercurrent disease	1 (<1)	1 (<1)
<b>TOTAL*</b>	<b>70 (15)</b>	<b>110 (22)</b>

\* $P < .001$

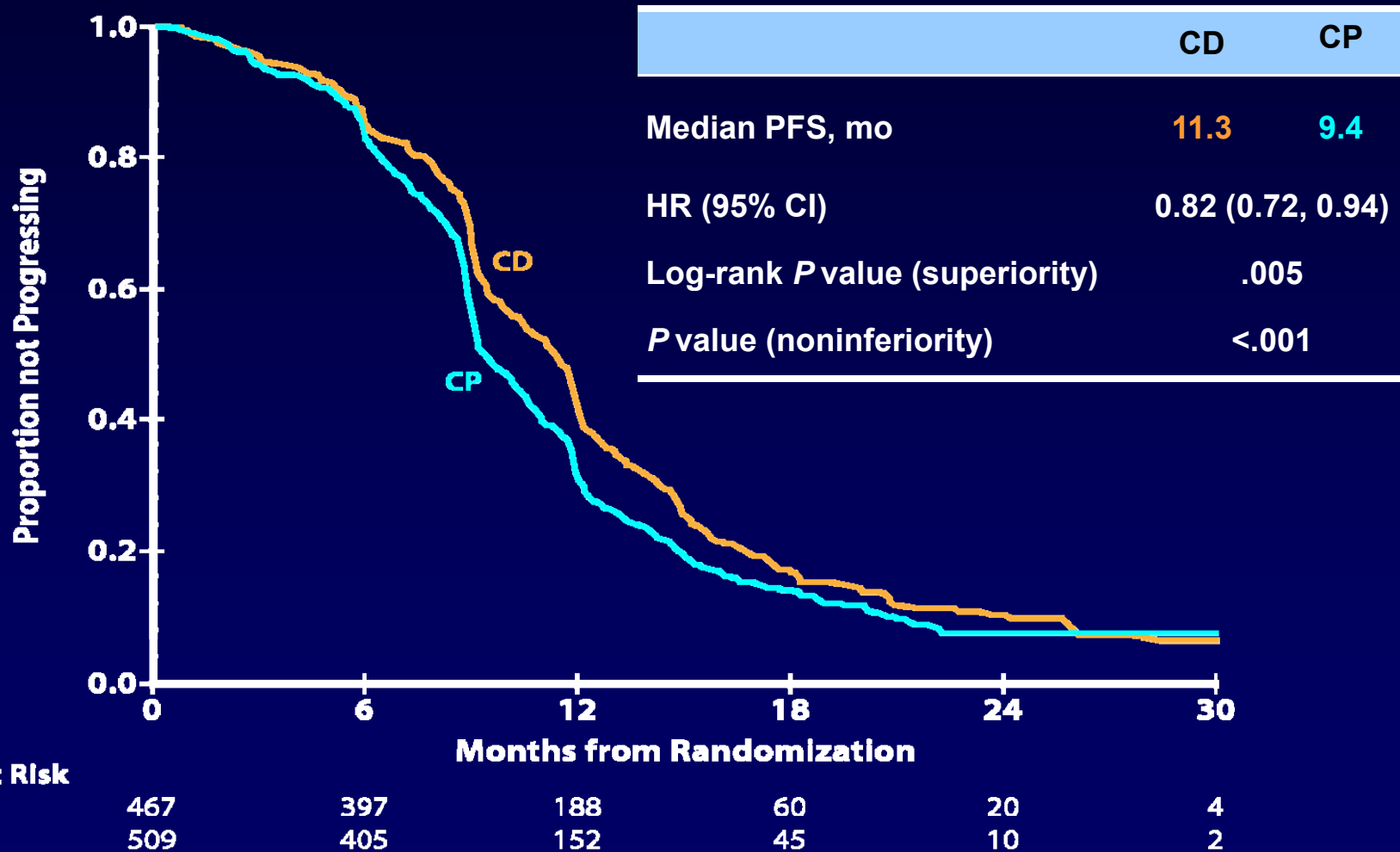
# Carboplatin Hypersensitivity Reactions

	CD (n = 466)		CP (n = 501)	
	Grade 2	Grade 3/5	Grade 2	Grade 3/5
Hypersensitivity*	3%	2%	10%	9%
One drug stopped		-	2%	
Both drugs stopped		1%	4%	

\* $P < .001$

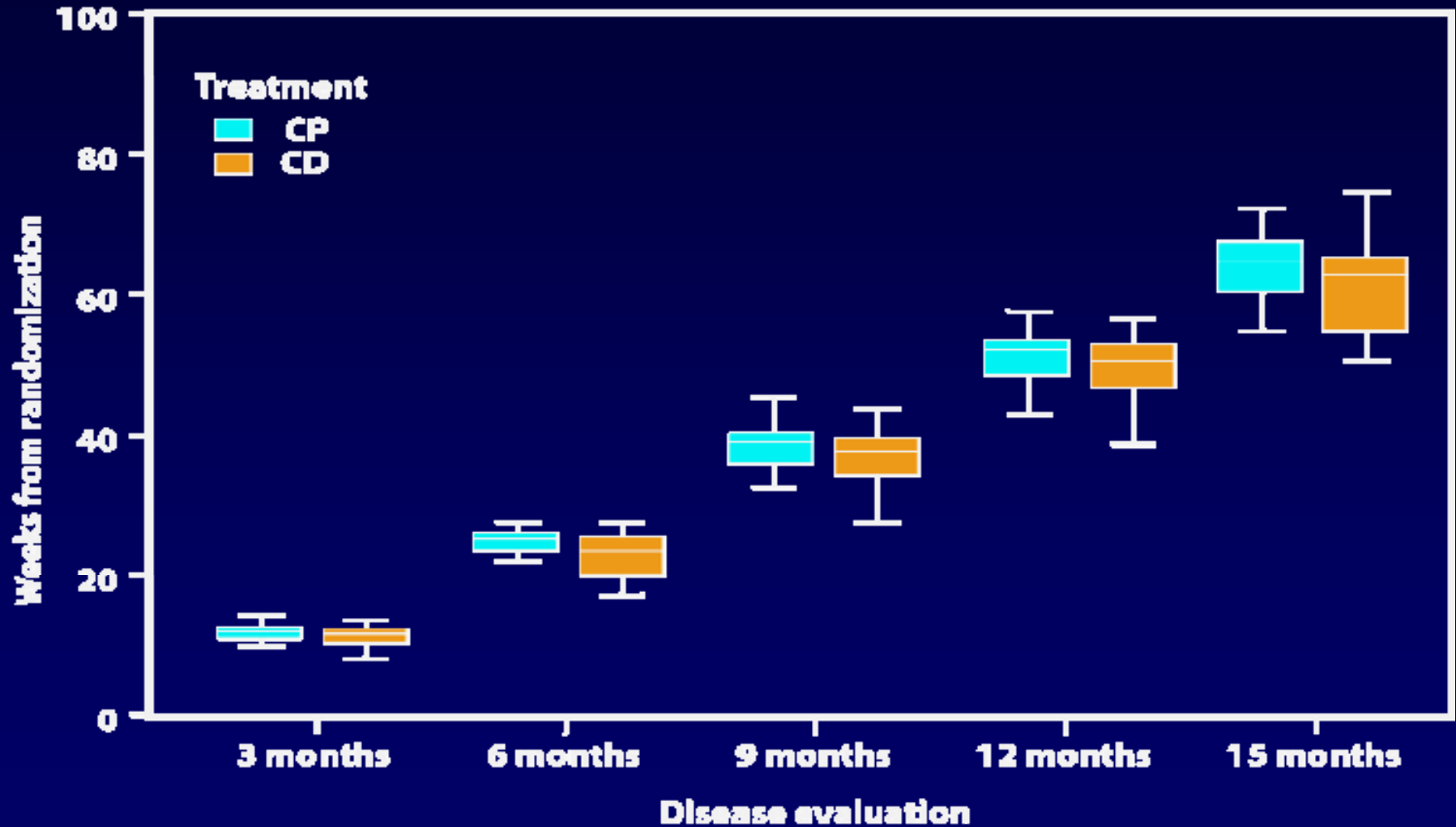
*Protocol included EORTC guidelines for rechallenge after a hypersensitivity reaction to carboplatin*

# Progression-Free Survival (ITT)



Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

# Symmetry of Tumor Assessments



Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

# Multivariate Analysis of Baseline Predictive Factors on PFS

## Significant Predictors of PFS Included

Baseline Factor		N	Multivariate Cox Regression Model		
			HR	95% CI	P Value
Therapy-free interval	6-12 months	342	1.00	(0.48, 0.65)	<.001
	>12 months	617	0.56		
Measurable disease	No	362	1.00	(1.27, 1.70)	<.001
	Yes	597	1.47		
CA 125	<100	316	1.00	(1.52, 2.07)	<.001
	≥100	643	1.77		
Treatment arm	CP	499	1.00	(0.71, 0.93)	.003
	CD	460	0.80		

# Platinum-Based Combination Therapies in Platinum-Sensitive Recurrent Ovarian Cancer

Paclitaxel + Carboplatin	Gemcitabine + Carboplatin	PLD + Carboplatin
Effective (PFS, OS)	Effective (PFS)	Effective (PFS) Superiority to carboplatin/paclitaxel
Schedule: d1 q 3 w	Schedule: d1 and 8 q 3 w	Schedule: d1 q 4 w
Neurotoxicity	Hematologic toxicity	Low toxicity
Alopecia 86%	Alopecia 15%	Alopecia 7%
QoL no worsening	QoL no worsening	QoL data pending

# Treatment Recommendation for Our Patient with Recurrence 6-12 Months

- There is level 1 evidence of two adequately powered studies that platinum-based combination therapy is superior to platinum monotherapy.
- There is level 1 evidence that a third platinum-based combination therapy is at least noninferior to one of the current standards of care and might even be superior (PFS). This combination is also less toxic.
- Based on efficacy data, possible pre-existing toxicities, weighting of possible new toxicities, and a convenient schedule, treatment with carboplatin and pegylated liposomal doxorubicin would be the treatment of choice.