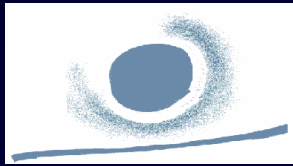


Changing Standards of Care: Recent Advances in the Management of Recurrent Ovarian Cancer

Eric Pujade-Lauraine, MD, PhD
Hôpital Hôtel-Dieu
Paris, France





What Do Patients Think About CA125 Monitoring in the Follow-Up? Results from a Multicenter Trial in 1060 Patients with Ovarian Cancer

Guelten Oskay-Oezcelik, Andreas du Bois, Peter Andreas Fasching , Sven Mahner, Clemens Liebrich, Anja Glaß, Sabine Schmidt- Wetzel, Leodolter Sepp, Karsten Muenstedt, W. Lichtenegger, and Jalid Sehoul

Which of the Following Methods Induce the Highest Anxiety? (Mark 3 Answers Maximum)

Primary

1. CA125	16%
2. Gyn. examination	14%
3. PAP	12%
4. Vaginal sonography	11%
5. Chest x-ray	6%
6. CT	3%
7. Abdominal sonography	2%
8. MRI	1%
9. PET	1%
10. Physical examination	0%

Relapsed

1. CA125	59%
2. Gyn. examination	13%
3. PAP	12%
4. Chest x-ray	12%
5. CT	8%
6. Abdominal sonography	4%
7. Vaginal sonography	1%
8. MRI	1%
9. PET	1%
10. Physical examination	0%

CA125 Definition of Progression Agreed by the Gynecologic Cancer Intergroup (GCIIG)

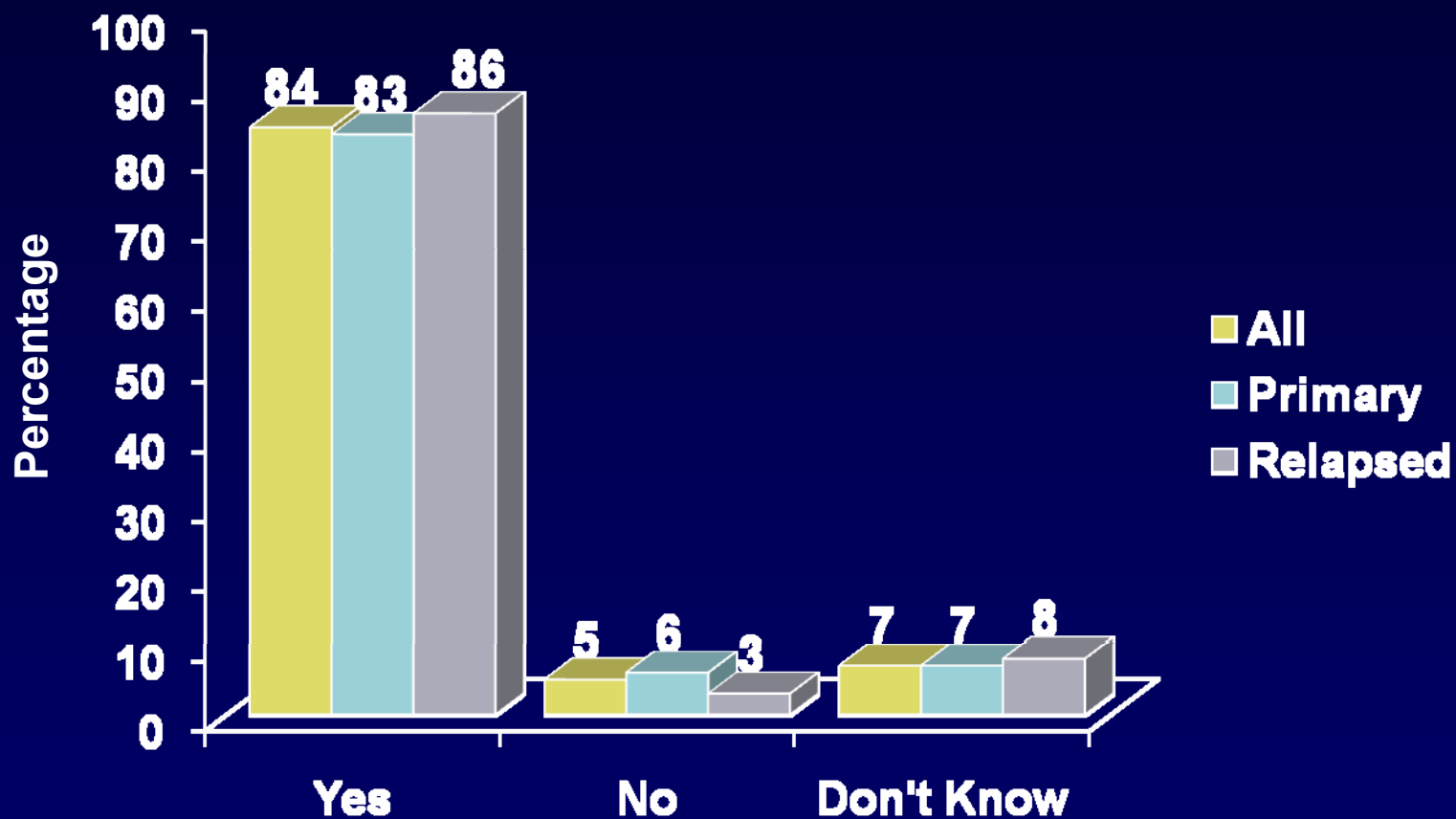


- ❖ CA125 $\geq 2x$ ULN or nadir value documented on TWO occasions (≥ 1 week)

ULN = upper limit of normal

Vergote I, et al. *J Natl Cancer Inst.* 2000;92(3):1534-1535.

Do You Expect a Longer Survival Period as a Result of Routine Follow-Up?



MRC OV05 and EORTC 55955



Early treatment of relapsed ovarian cancer
based on CA125 level alone

versus

Delayed treatment based on conventional clinical
indicators

Gordon Rustin

Trial Design

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

REGISTER

Blinded CA125 measured every 3 months

CA125 >2 x upper limit of normal
RANDOMIZED

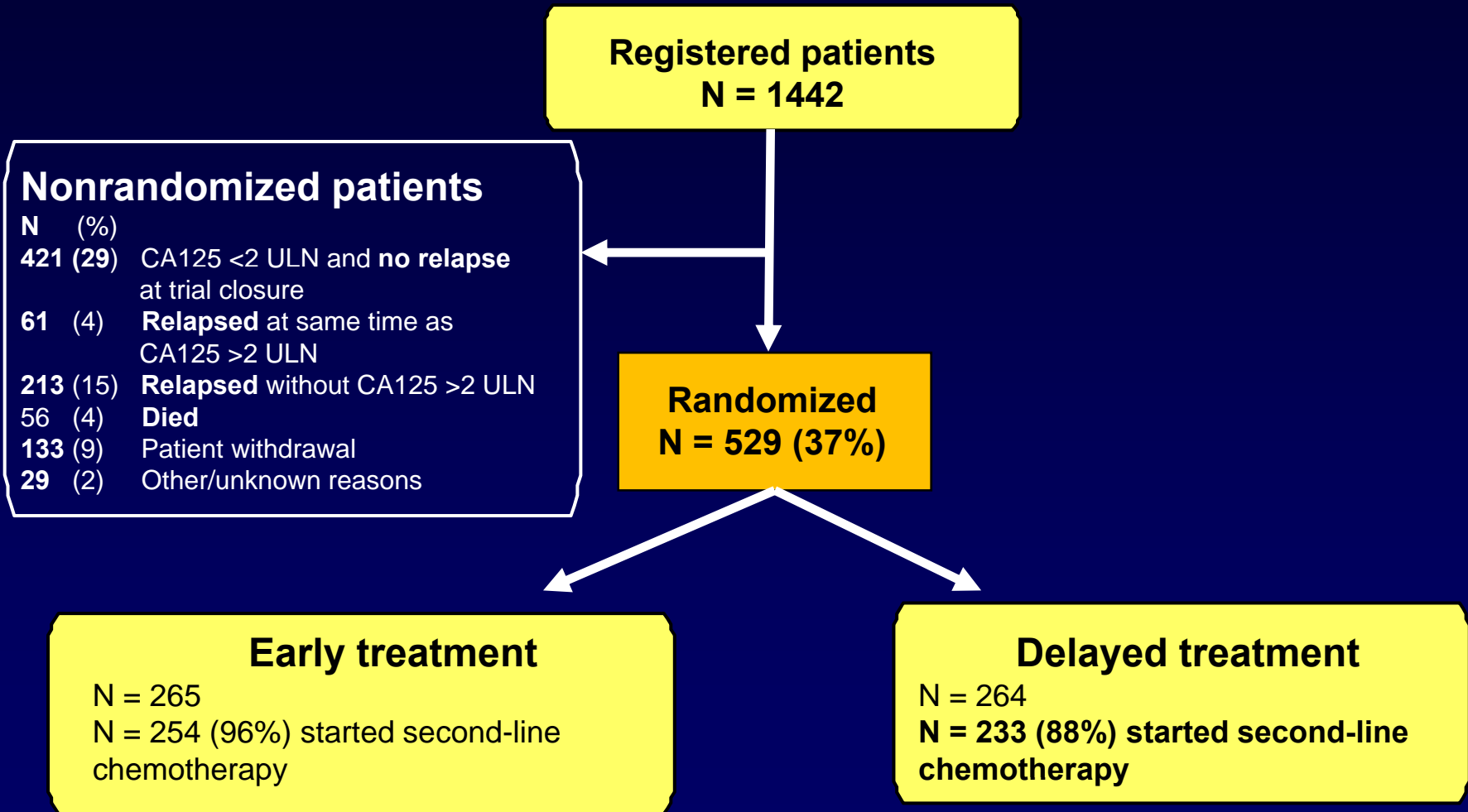
Early treatment

Clinician and patient informed

Delayed treatment

Clinician not informed, treatment delayed until clinically indicated

Trial Profile

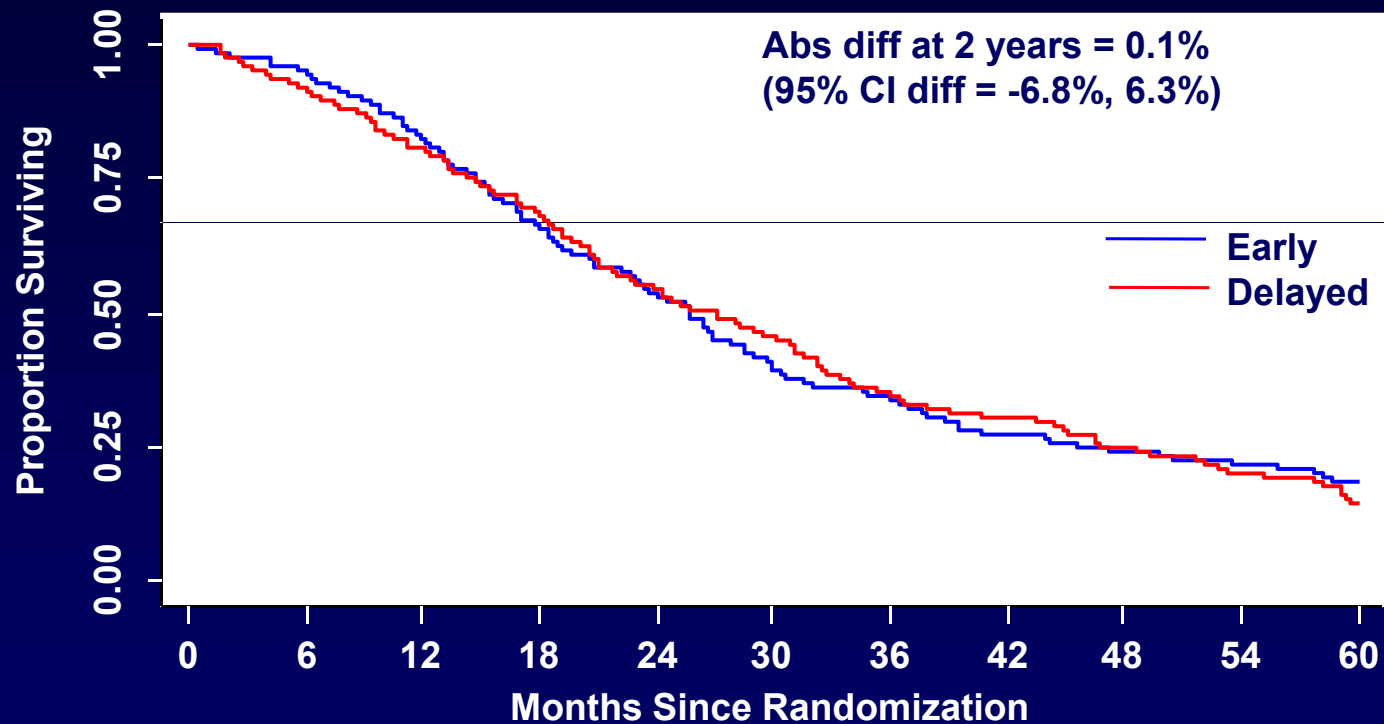


Outcome Measures and Sample Size

- **Primary outcome measure**
 - **Overall Survival**
- **Secondary outcome measures**
 - Time to second-line treatment
 - Time to third-line treatment or death
 - Quality of life (QoL)
- **Sample size**
 - To detect a 10% improvement in 2-year overall survival with early treatment (5% significance level and 85% power)
 - Study required
 - 345 events (deaths from all causes)
 - 1400 registered patients

Overall Survival

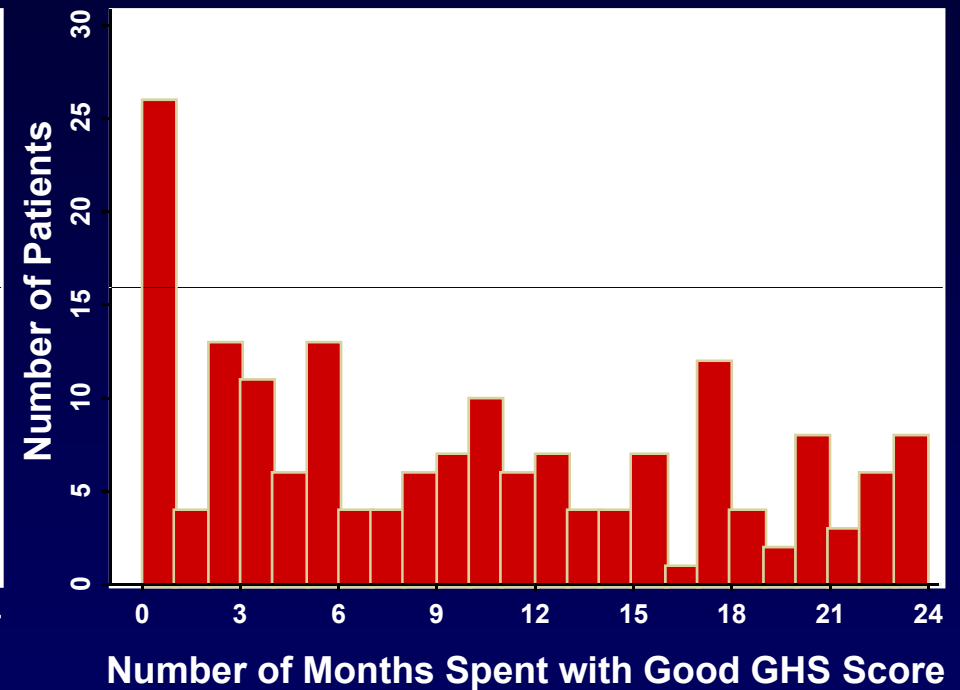
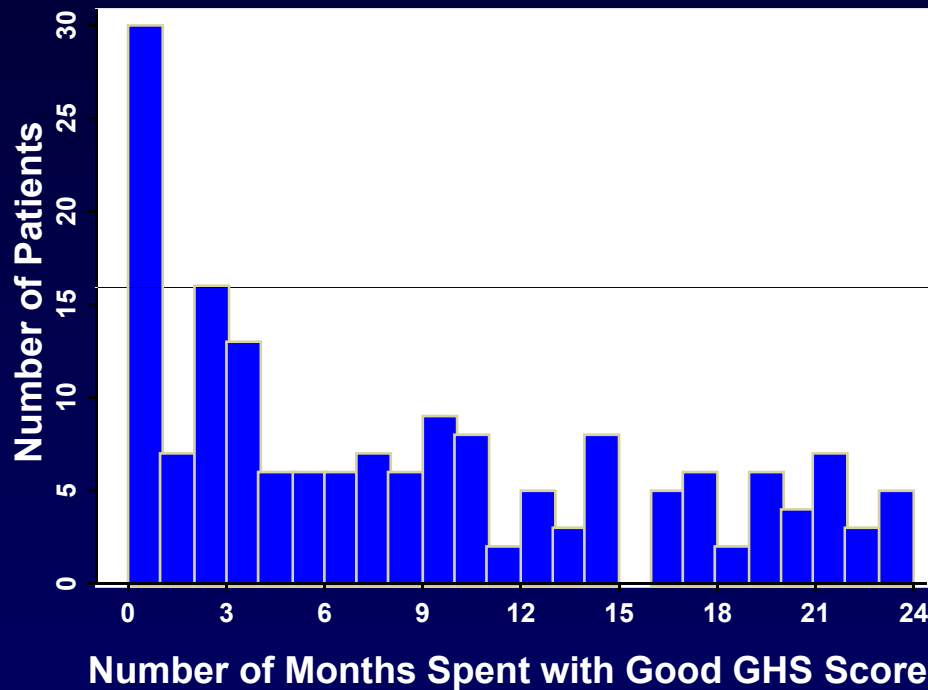
HR = 1.00 (95%CI 0.82-1.22) P = .98



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

Overall Time Spent with 'Good' GHS



	Median, months
■ Early	7.1
■ Delayed	9.2
	<i>P</i> = .15 (Mann-Whitney test)

GHS = global health score

Rustin G, et al. *J Clin Oncol.* 2009;27(18S): Abstract 1.

Conclusions

- **Early treatment did not improve overall survival**
 - HR = 1.00, 95% CI 0.82-1.22, $P = .98$
 - Absolute difference at 2 years 0.1% (95%CI -6.8%, 6.3%)
- **Early chemotherapy does not improve QoL**

How Should This Trial Influence Practice?

- Women can be reassured that
 - There is **no benefit from early detection of relapse** by routine CA125 measurements
 - Even if CA125 rises, **chemotherapy can be delayed until signs or symptoms of tumor recurrence**
- Women can be offered **informed choices** in follow-up
 - **No routine CA125 measurements** but rapid access to CA125 testing if symptoms or signs of relapse
 - **Regular CA125 measurements**

What Factors Influence the Decision to Treat When the CA125 Level Rises?

- **The level of CA125 (GCIIG definition of progression)**

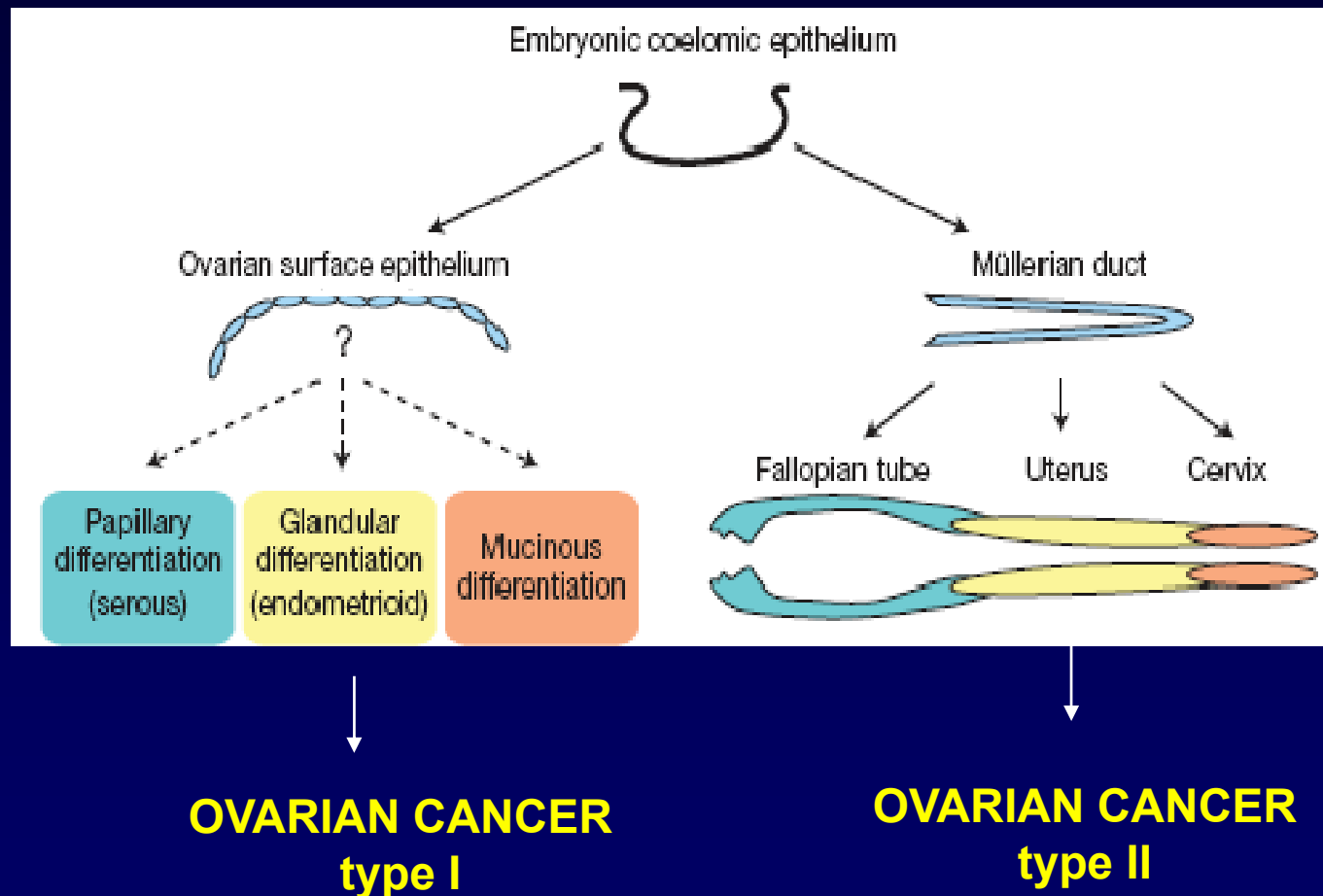
Multivariate Analysis of Disease-Related Predictive Factors on PFS in CALYPSO Trial (n = 976)

Multivariate Cox Regression Model				
Baseline Factor	N	HR	95% CI	P Value
	< 100	1.00		
CA 125	≥100-<1000	1.74	(1.52, 2.07)	<.001
	> 1000	2.11	(1.68, 2.66)	

What Factors Influence the Decision to Treat When the CA125 Level Rises?

- The level of CA125 (GCIIG definition of progression) **and its kinetics**

Embryonic Coelomic Differentiation

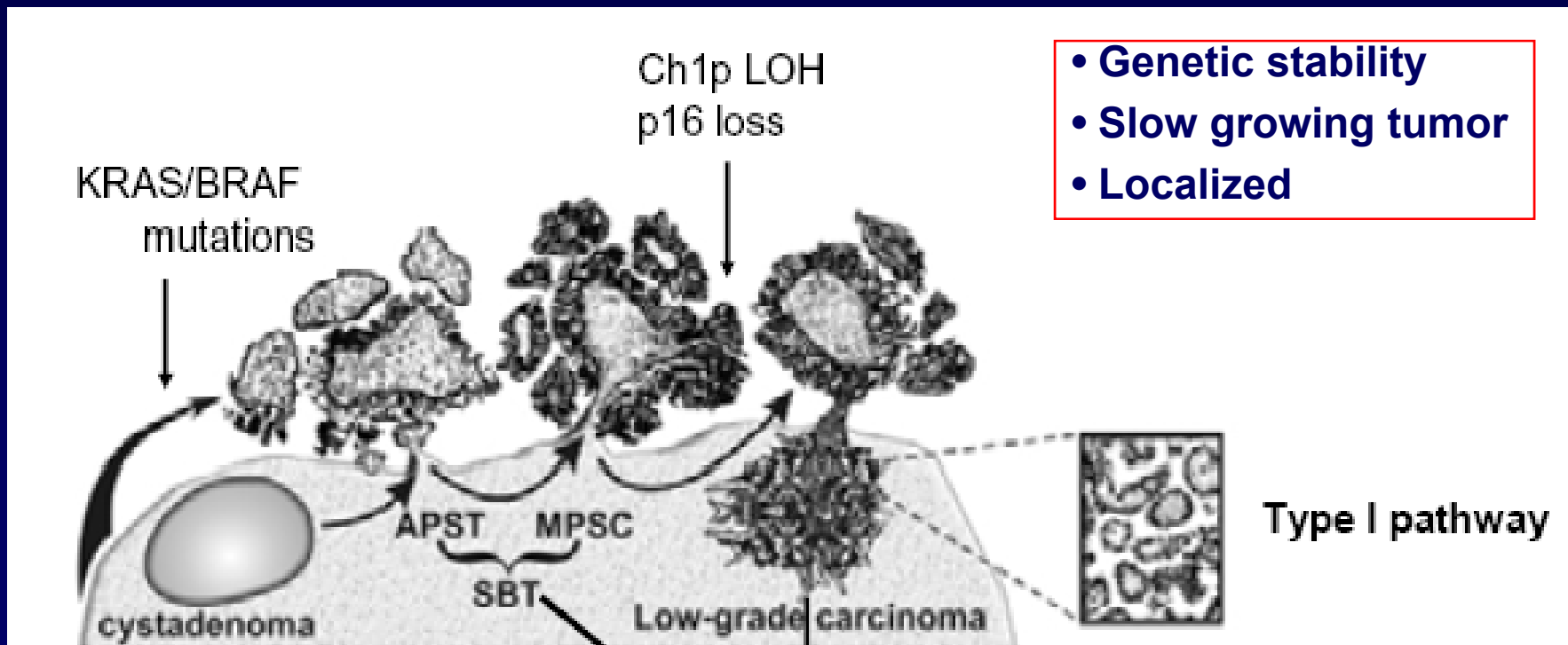


Cho KR et al. *Ann Rev Pathol.* 2009;4:287-313.

Kurman R et al. *Int J Gynecol Pathol.* 2008;27(2):151-160.

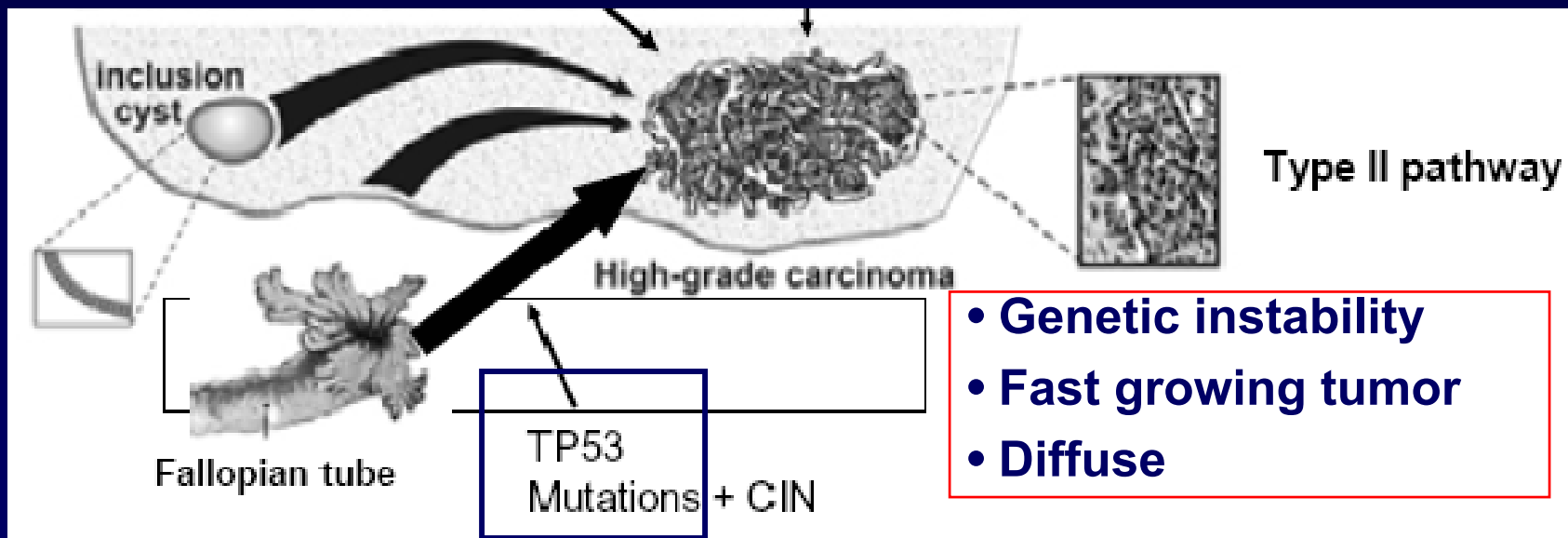
Ovarian Cancer Type I

- Suspected origin: Ovarian surface epithelium
- Histologic type: - Low grade serous & endometrioid
 - Mucinous
 - Clear cell

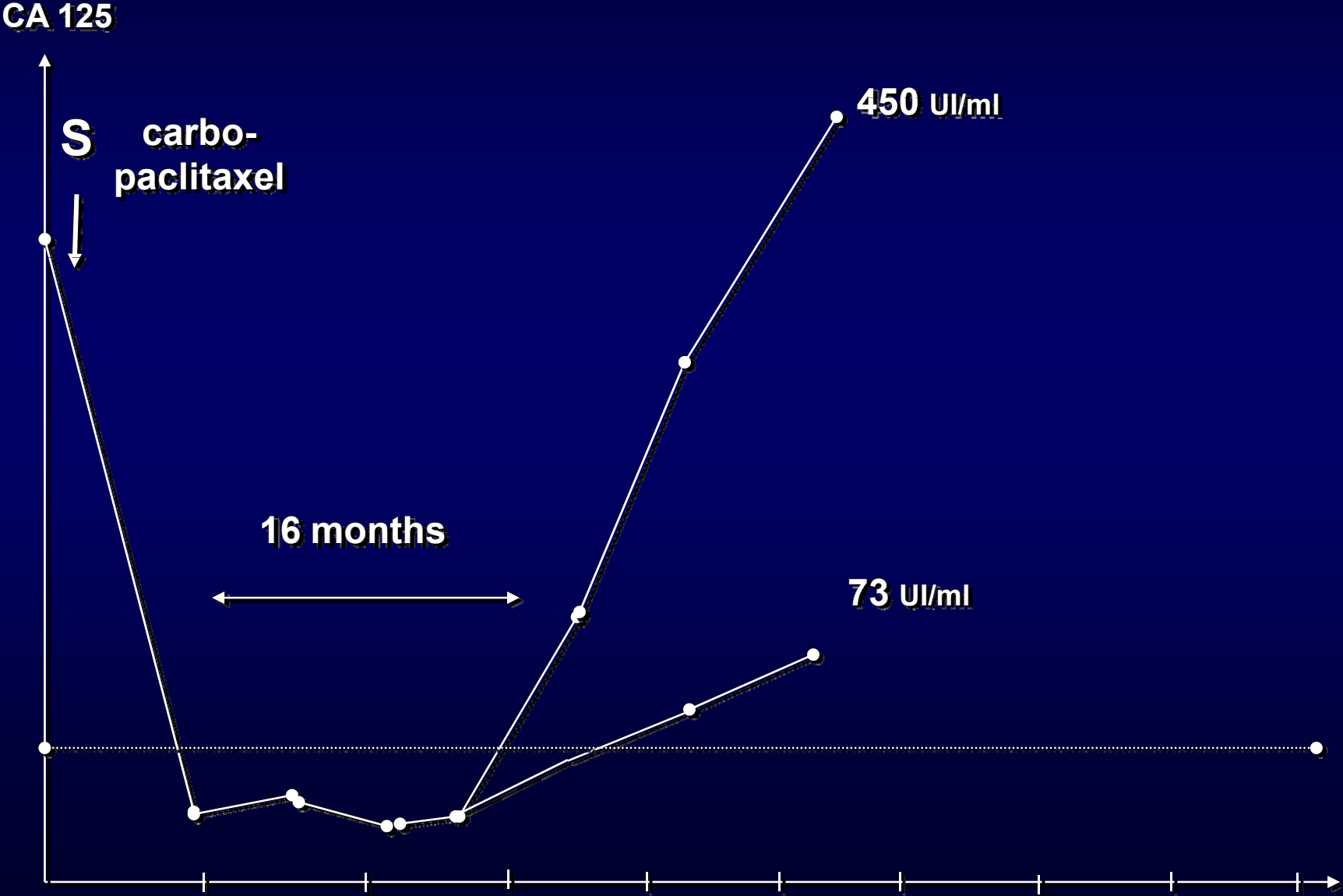


Ovarian Cancer Type II

- Suspected origin: **Fallopian tube**, epithelium, inclusion cyst
- Histologic type: - **High grade serous & endometrioid**
 - Undifferentiated



Kinetics of CA125 Rise in Slow-Growing and Fast-Growing Ovarian Cancer



What Factors Influence the Decision to Treat When the CA125 Level Rises?

- The level of CA125 (GCIg definition of progression) and its kinetics
- **Disease-related prognostic factors**

Multivariate Analysis of Disease-Related Predictive Factors on PFS in CALYPSO Trial (n = 976)

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		
CA125	<100	316	1.00	(1.52, 2.07)	<.001
	≥100	643	1.77		

What Factors Influence the Decision to Treat When the CA125 Level Rises?

- The level of CA125 (GCIIG definition of progression) and its kinetics
- Disease-related prognostic factors
- Patient age, performance status, comorbidities

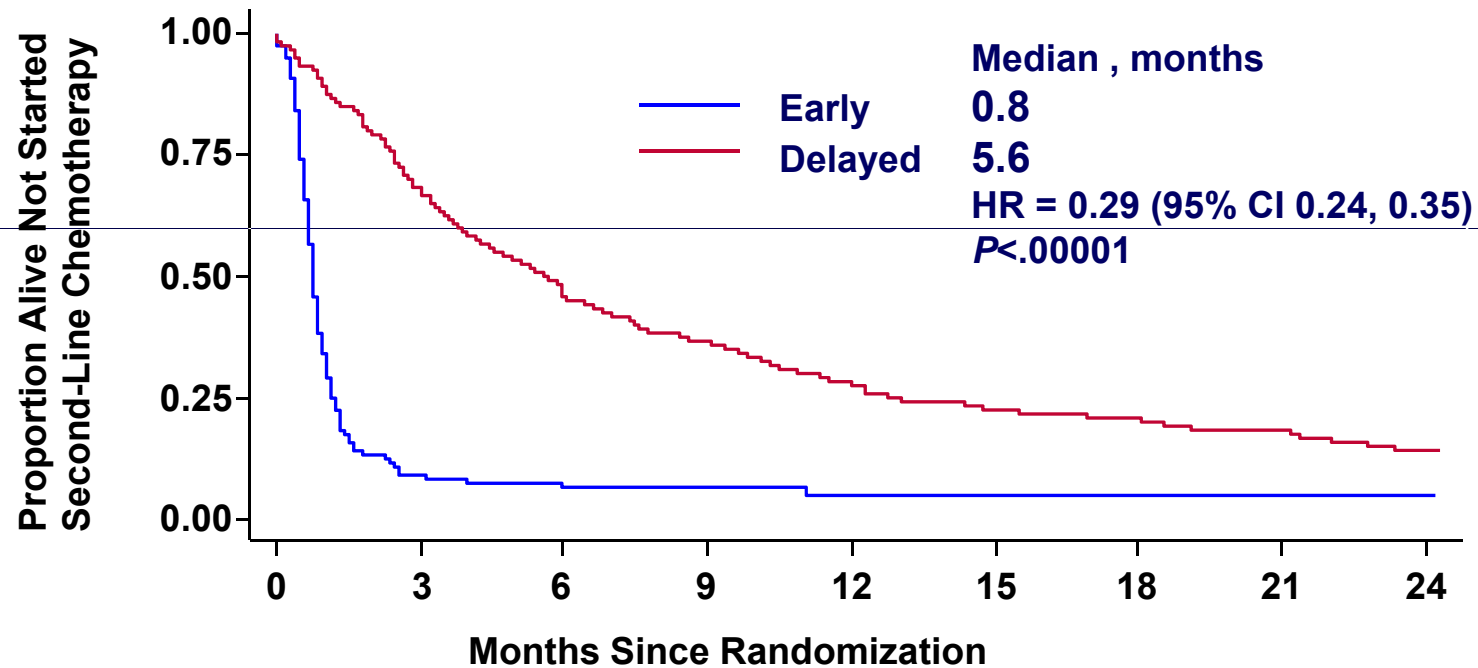
What Factors Influence the Decision to Treat When the CA125 Level Rises?

- The level of CA125 (GCIIG definition of progression) and its kinetics
- Disease-related prognostic factors
- Patient age, performance status, comorbidities
- Patient wish

What Factors Influence the Decision to Treat When the CA125 Level Rises?

- The level of CA125 (GCIIG definition of progression) and its kinetics
- Disease-related prognostic factors
- Patient age, performance status, comorbidities
- Patient wish
- Patient symptoms

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

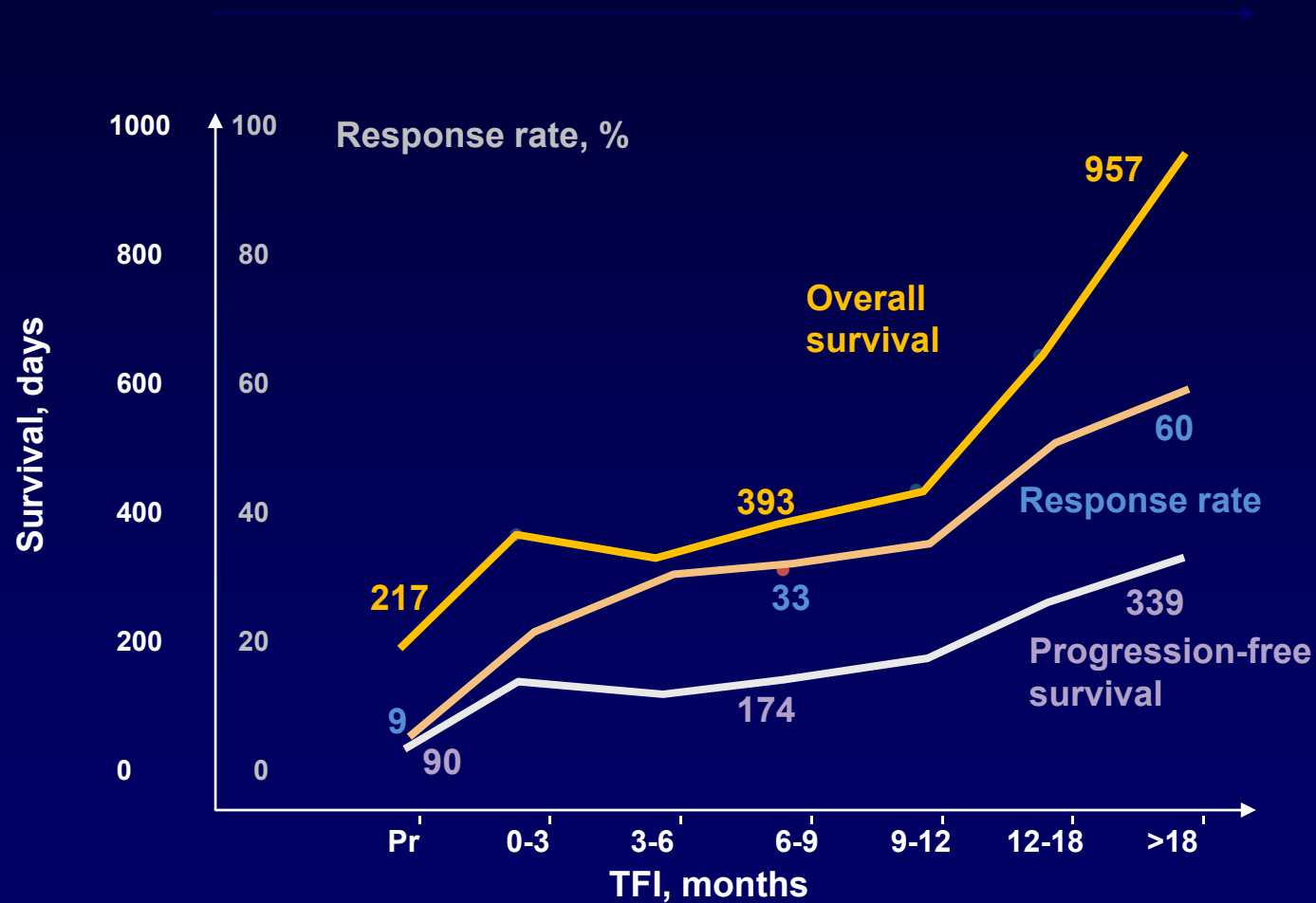
Conclusion

- **CA125 helps to screen (and spare) imagery tests to confirm a suspicion of relapse**
- **CA125 rises should not be the sole factor for treatment decision**

Patient Outcome in Relapse Depends On:

- **Therapy-free interval**

Outcome by Treatment-Free Interval (TFI)



Patient Outcome in Relapse Depends On:

- Therapy-free interval
- **And treatment!**

The Traditional Treatment Paradigm

Recurrence After First-Line Chemotherapy

**Platinum
Refractory/Resistant**



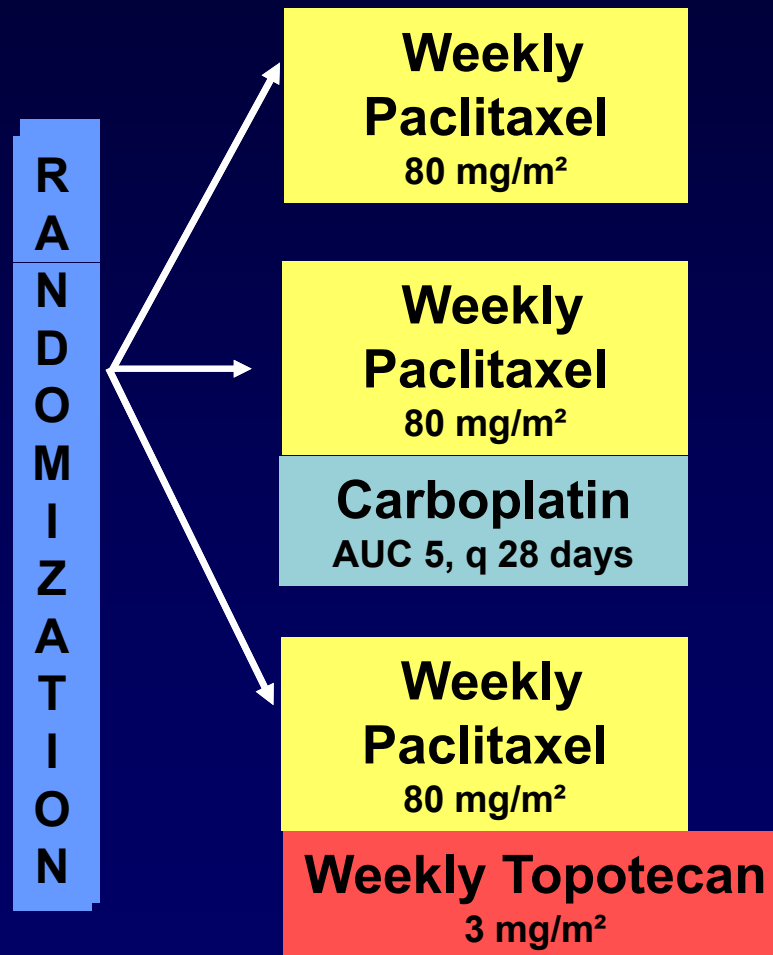
<6 Months



**Nonplatinum
Treatment**

Regimen Administered	Early N (%)	Delayed N (%)
Combination platinum	131 (49)	134 (51)
Combination platinum (no taxane)	40 (15)	33 (13)
Platinum + taxane based	91 (34)	101 (38)
Carboplatin alone	78 (29)	67 (25)
Nonplatinum regimens	43 (17)	24 (9)
Taxane without platinum	15 (6)	9 (3)
Other	28 (11)	15 (6)
Absence of defined treatment	13 (5)	39 (15)
Unknown treatment	2 (1)	8 (3)
No treatment given	11 (4)	24 (9)
Not yet given (no clinical relapse)	0	7 (3)
Total	265	264

Resistant Relapse: Single-Agent Versus Doublets—GINECO Trial



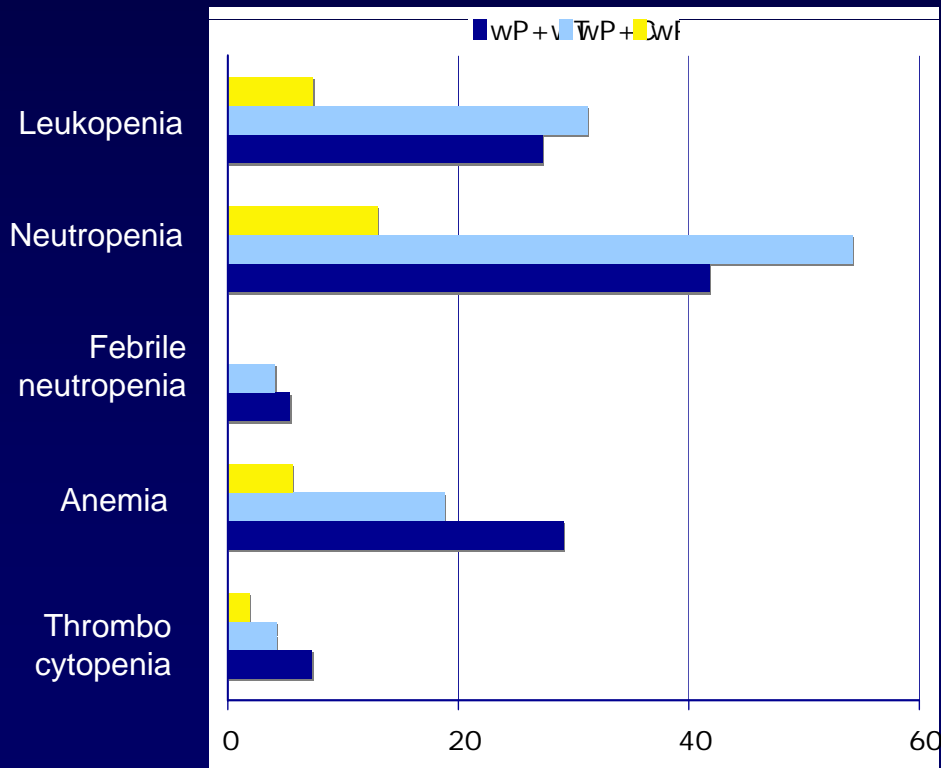
Discontinuation from drug treatment for toxicity :

wP : 1.9 %

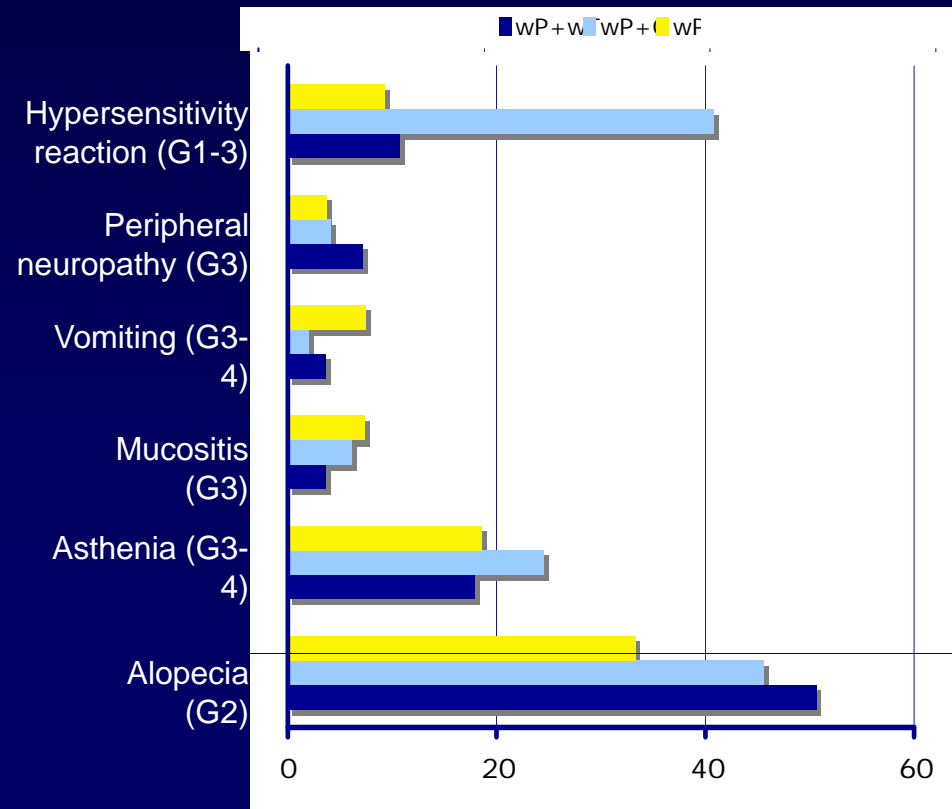
wP+C : 29.4 %

wP+wT : 22.8 %

Grade 3-4 Hematologic Toxicities



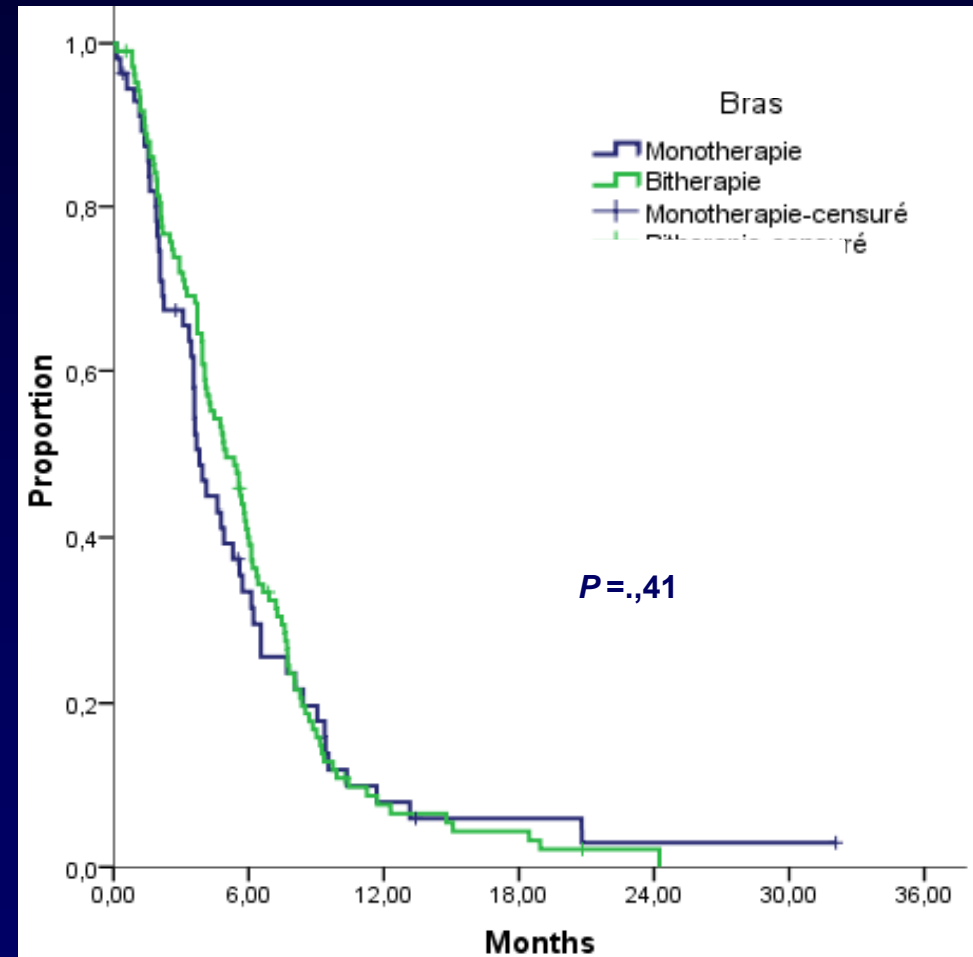
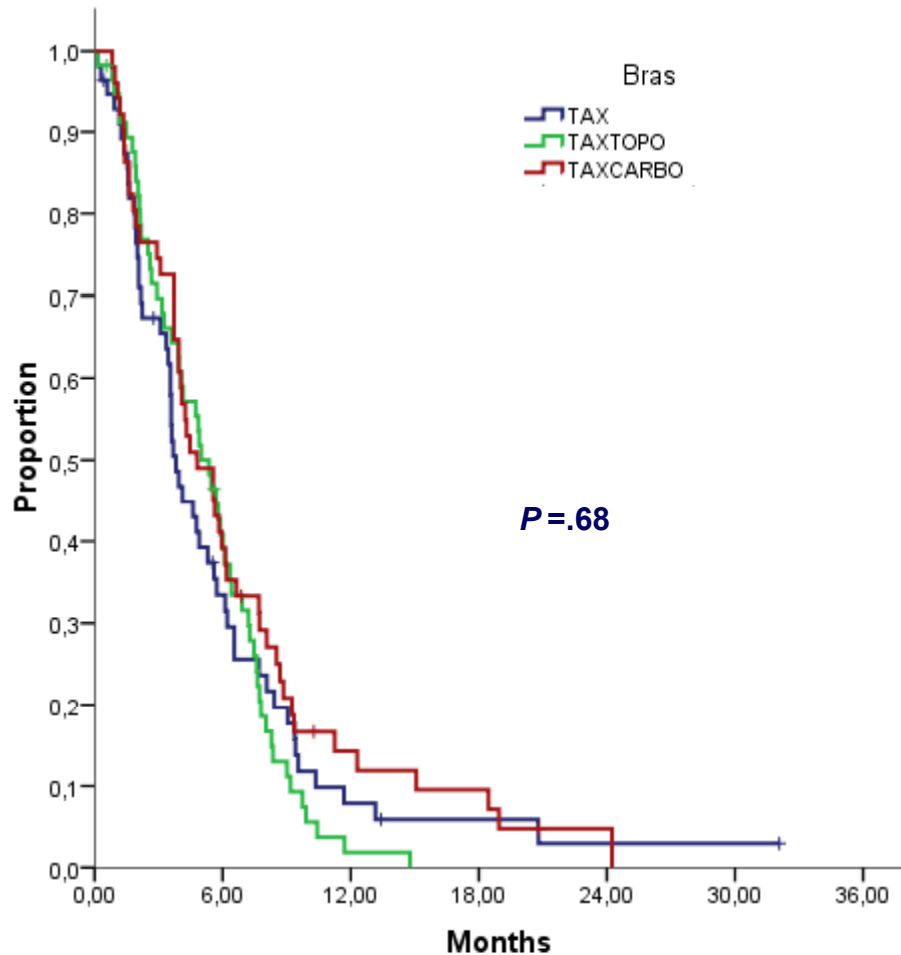
Nonhematologic Toxicities



Response Rate (% of Patients)

	wP (N = 57)	wP+C (N = 51)	wP+wT (N = 57)
Response (complete + partial)	35.1	37.3	38.6
Stable disease	22.8	29.4	22.8
Progression	26.3	25.5	24.6
Nonevaluable	15.8	7.8	14

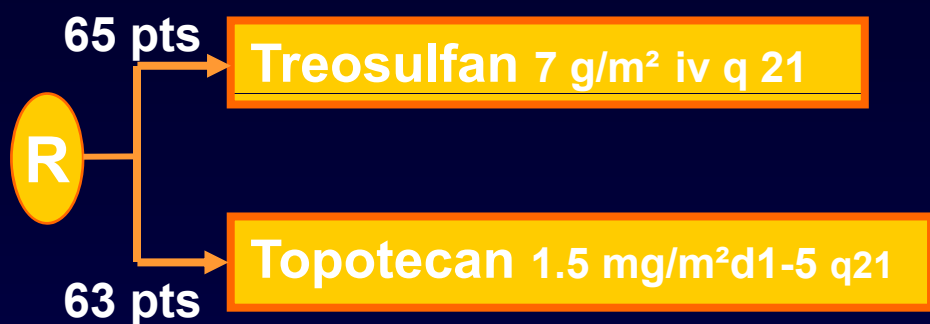
Progression-Free Survival



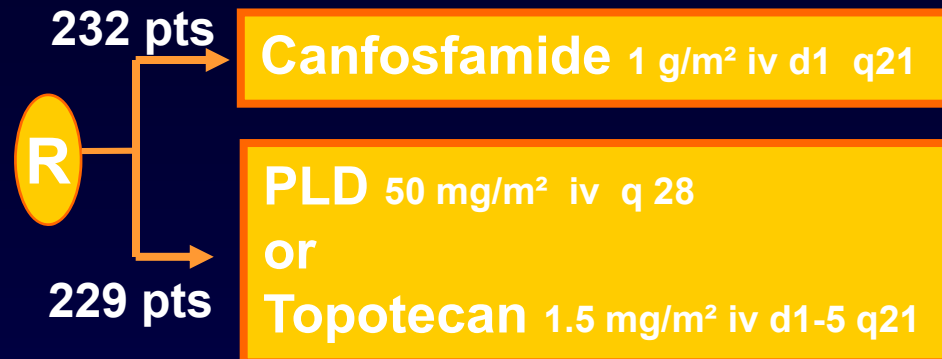
monotherapy (wP) vs bithérapie (wP+C or wP+wT)

Resistant Disease: Available Agents

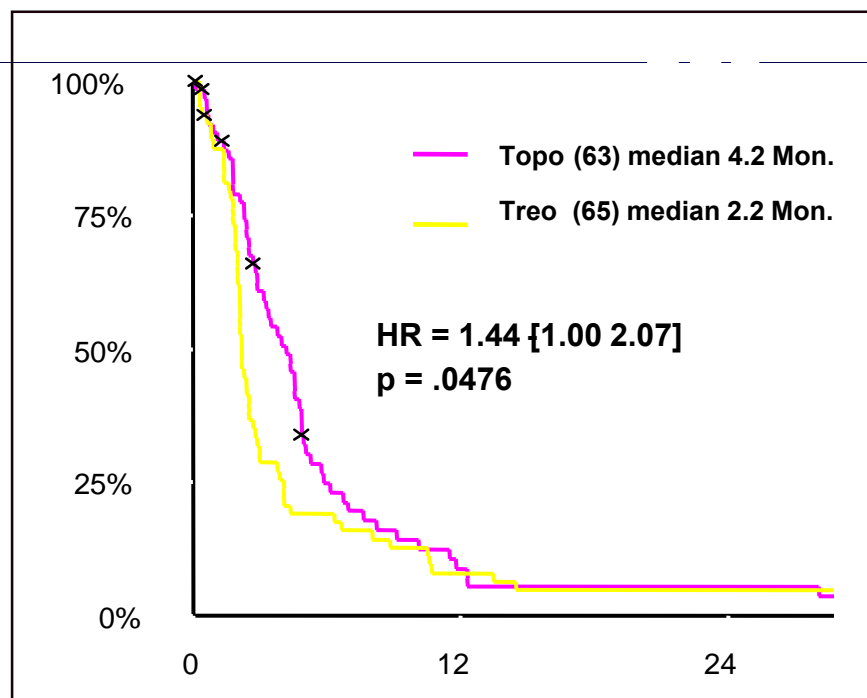
Agent	No of Patients	Response Rate
Pegylated liposomal doxorubicin	428	18%
Topotecan	882	17%
Paclitaxel	1580	22%
Oral etoposide	234	31%
Gemcitabine	181	18%
Hexamethylmelamine	235	18%
Oxaliplatin	118	23%
Vinorelbine	71	23%



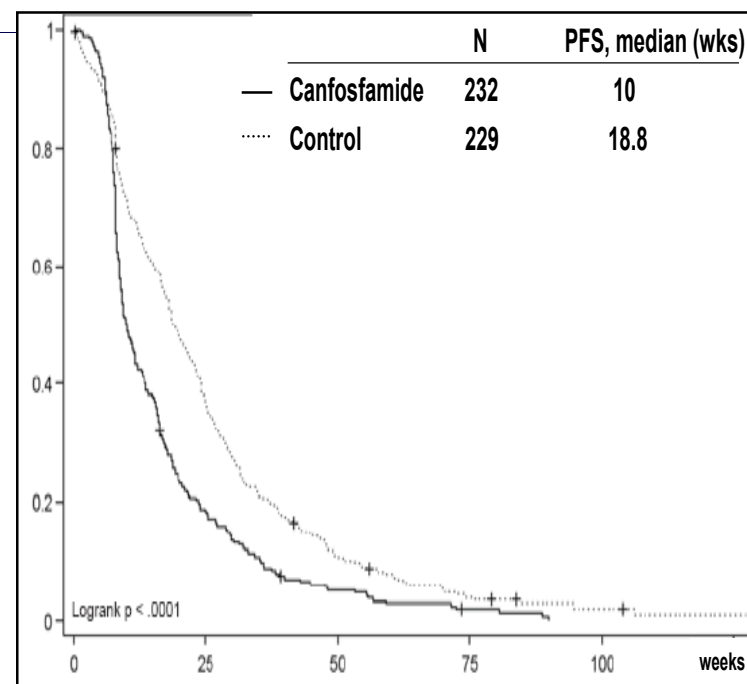
Meier W, et al. ASCO. 2003¹



Vergote I, et al. ASCO. 2007²



OR 19.3% (topo) vs 7.0% (p=.0524)



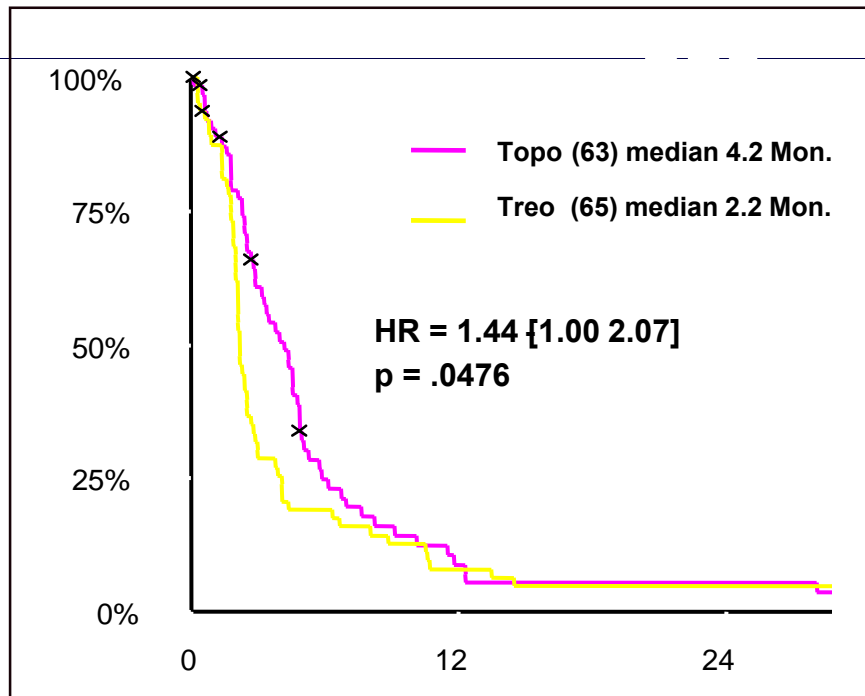
1. Meier W, et al. *Proc Am Soc Clin Oncol*. 2003;22: Abstract 1810. 2. Vergote I, et al. *J Clin Oncol*. 2007;25(18S): Abstract LBA5528.



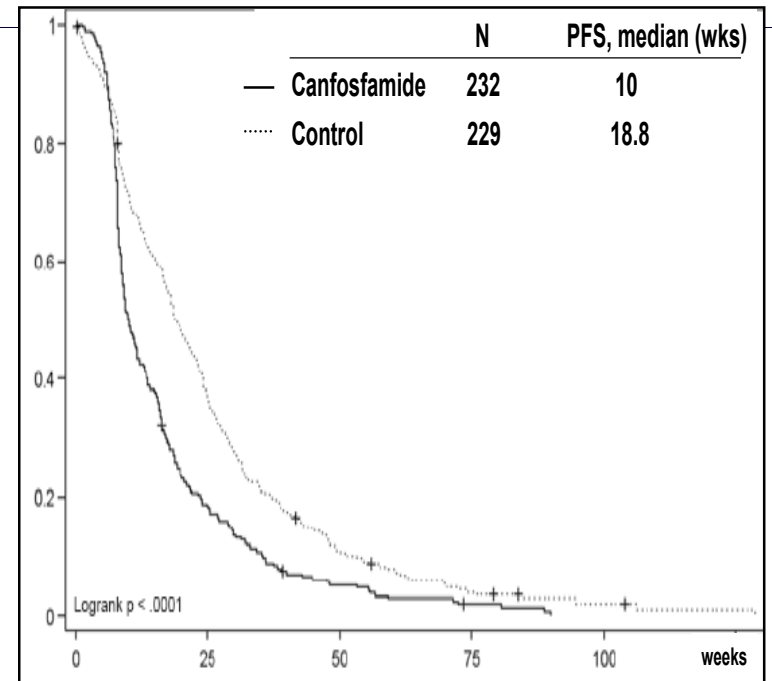
Meier W, et al. ASCO. 2003¹



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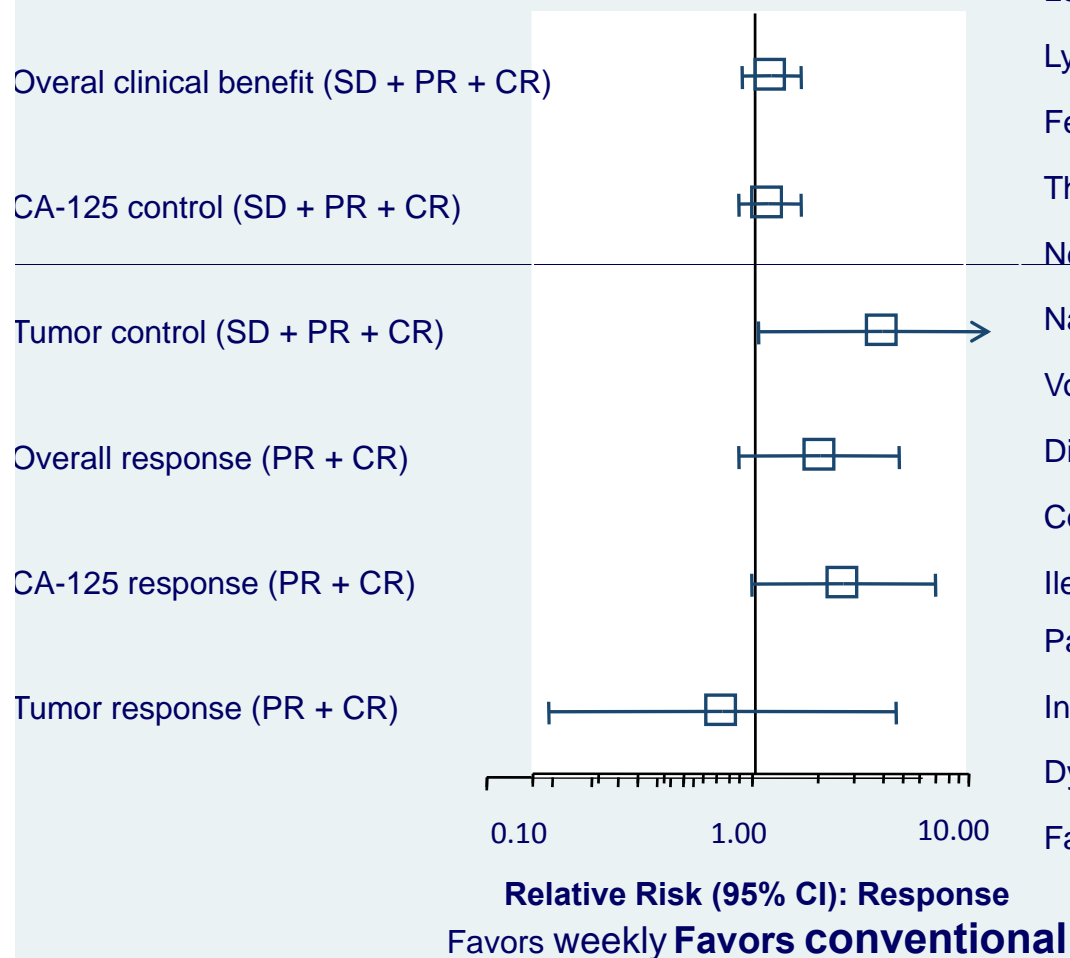
1. Meier W, et al. *Proc Am Soc Clin Oncol*. 2003;22: Abstract 1810. 2. Vergote I, et al. *J Clin Oncol*. 2007;25(18S): Abstract LBA5528.

Topotecan Weekly (4 mg/m²/wk)
versus
Routine 5-day Schedule (1.25 mg/m²/d x 5)
in Patients with Platinum-Resistant
Ovarian Cancer (TOWER):
A Randomized, Multicenter Trial of the
North-Eastern German Society of
Gynaecological Oncology (NOGGO)

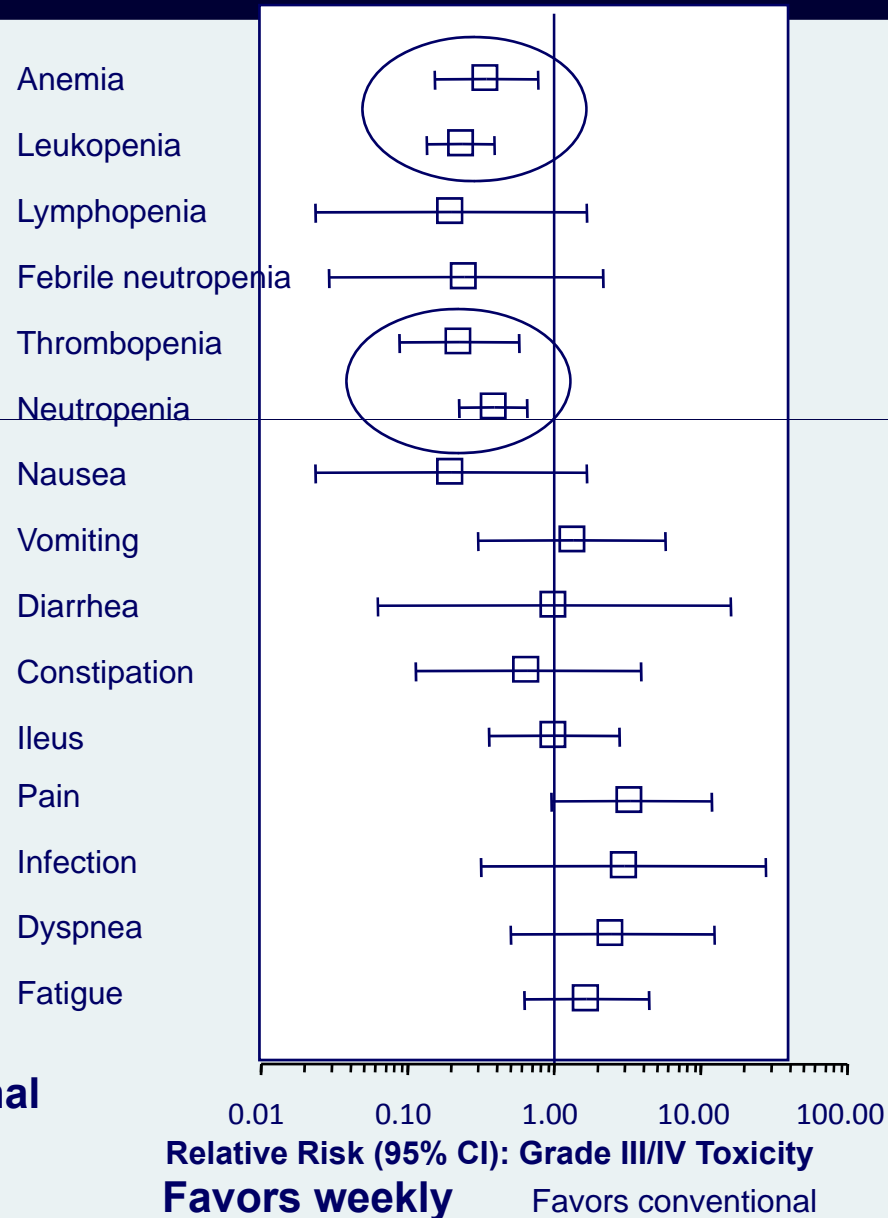
WWW.NOGGO.de

- PI: Prof. Jalid Sehouli

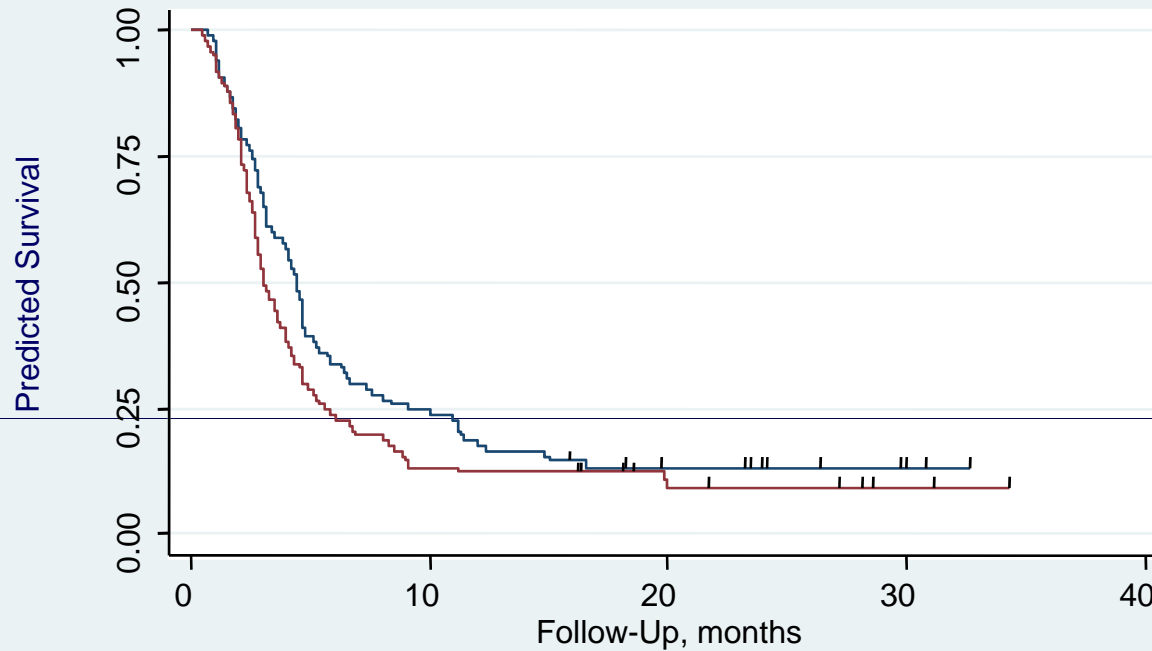
Responses by Subgroups



Toxicities

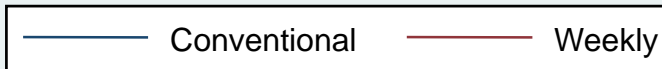


Progression-Free Survival



Number at risk

Conventional	97	24	10	3	0
Weekly	97	13	7	2	0



Log-rank test $P = .084$

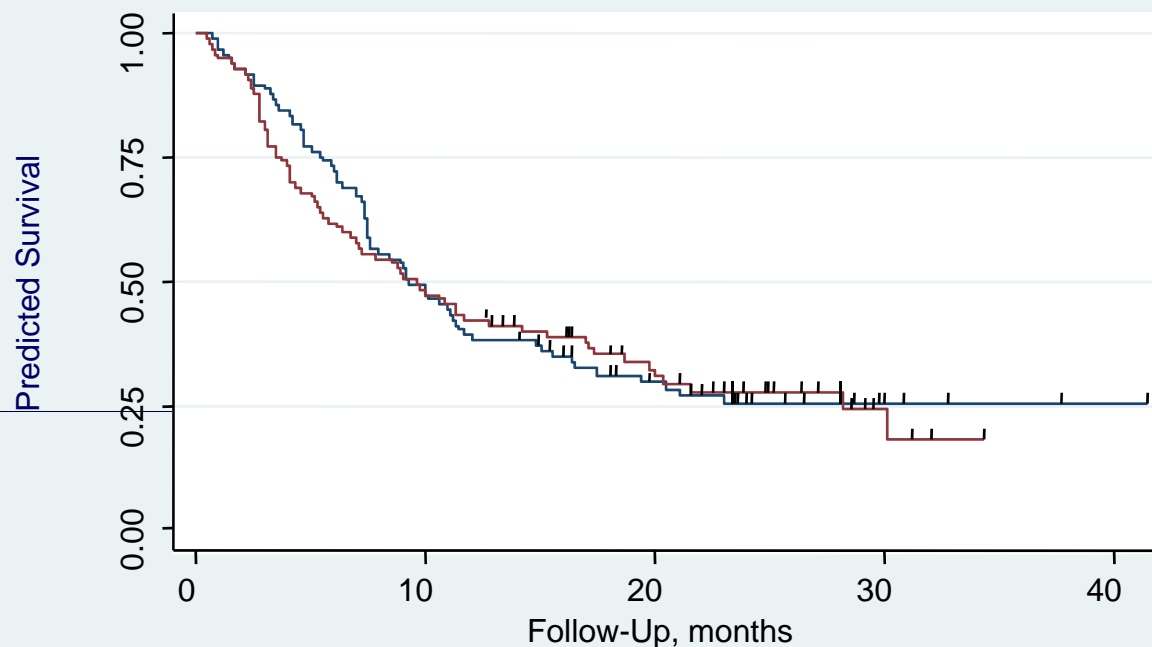
$HR_{w:c} 1.29$ (95% CI 0.96 – 1.76), $P = .088$

Predicted survival, months

	Median	95% CI	
Weekly	3.0	2.7	3.9
Conventional	4.4	3.4	4.8

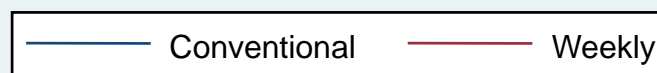
Sehouli J, et al. *J Clin Oncol.* 2009;25(15S): Abstract 5553.

Overall Survival



Number at risk

Conventional	97	48	21	5	1
Weekly	97	47	23	4	0



Log-rank test $P = .831$

HR_{w:c} 1.04 (95% CI 0.74 – 1.45)

Predicted survival, months

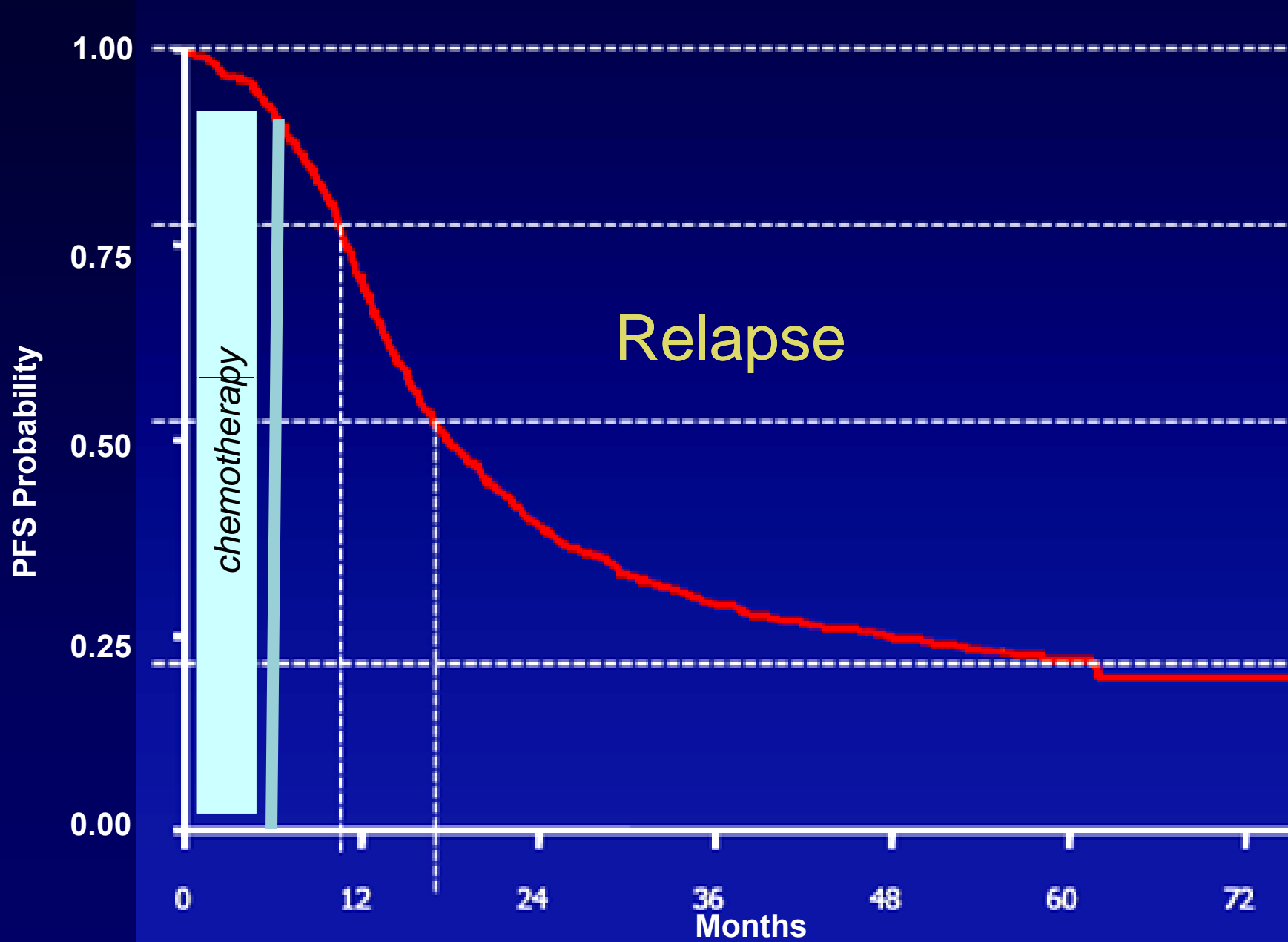
	Median	95% CI	
Weekly	9.6	6.3	14.2
Conventional	9.3	7.5	11.4

Sehoul J, et al. *J Clin Oncol*. 2009;25(15S): Abstract 5553.

Resistant Patients

- **Monotherapy remains standard**
- **Type of drug and schedule influence patient tolerance and outcome**
- **Cytotoxic drugs should be explored with targeted therapy**

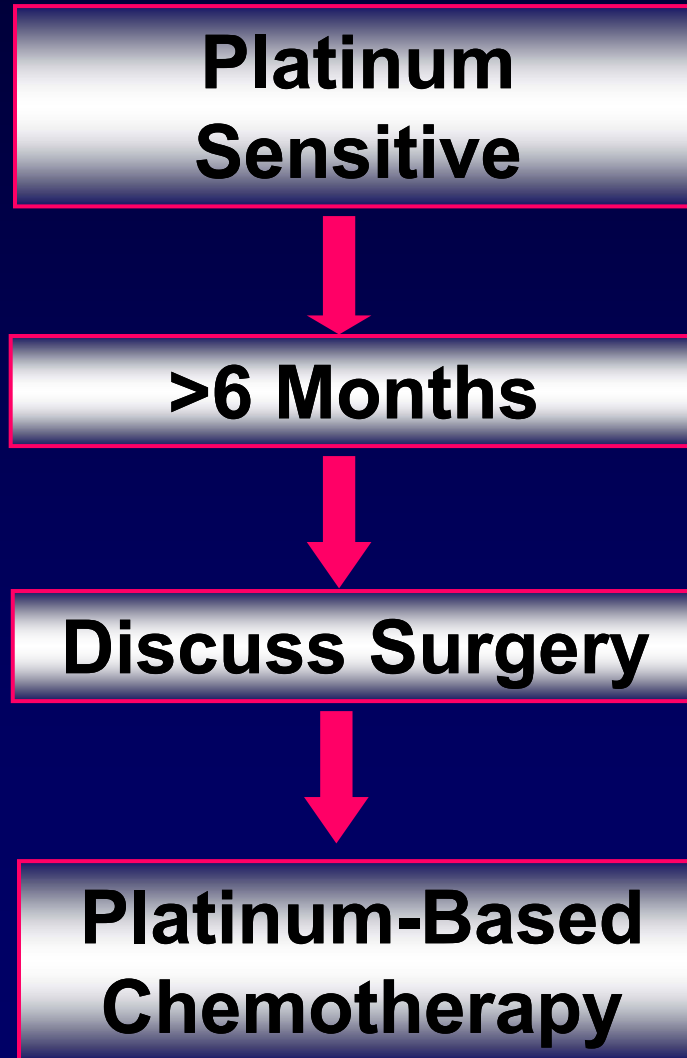
AGO Ovar 3



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

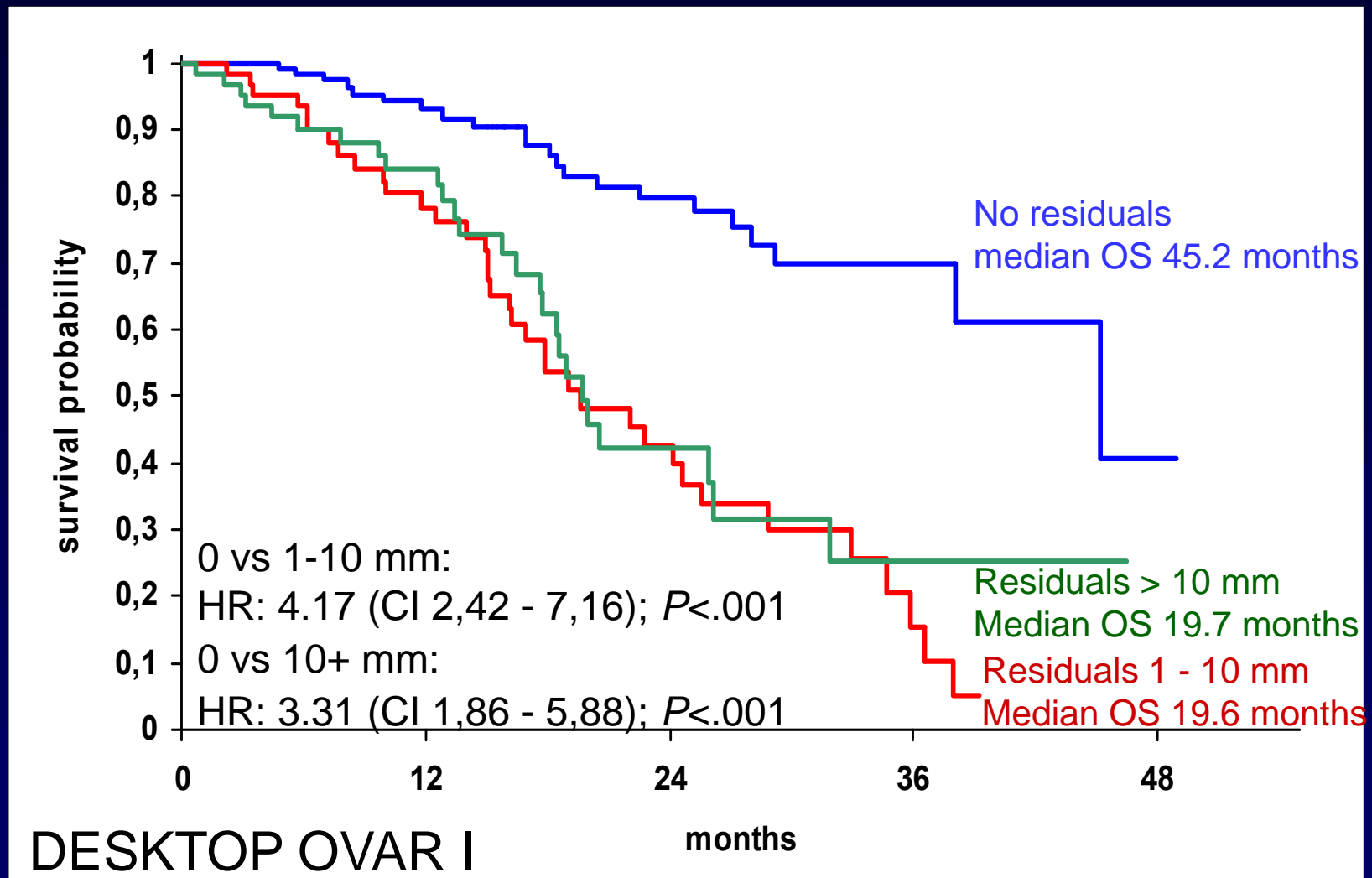
The Traditional Treatment Paradigm

Recurrence After First-Line Chemotherapy



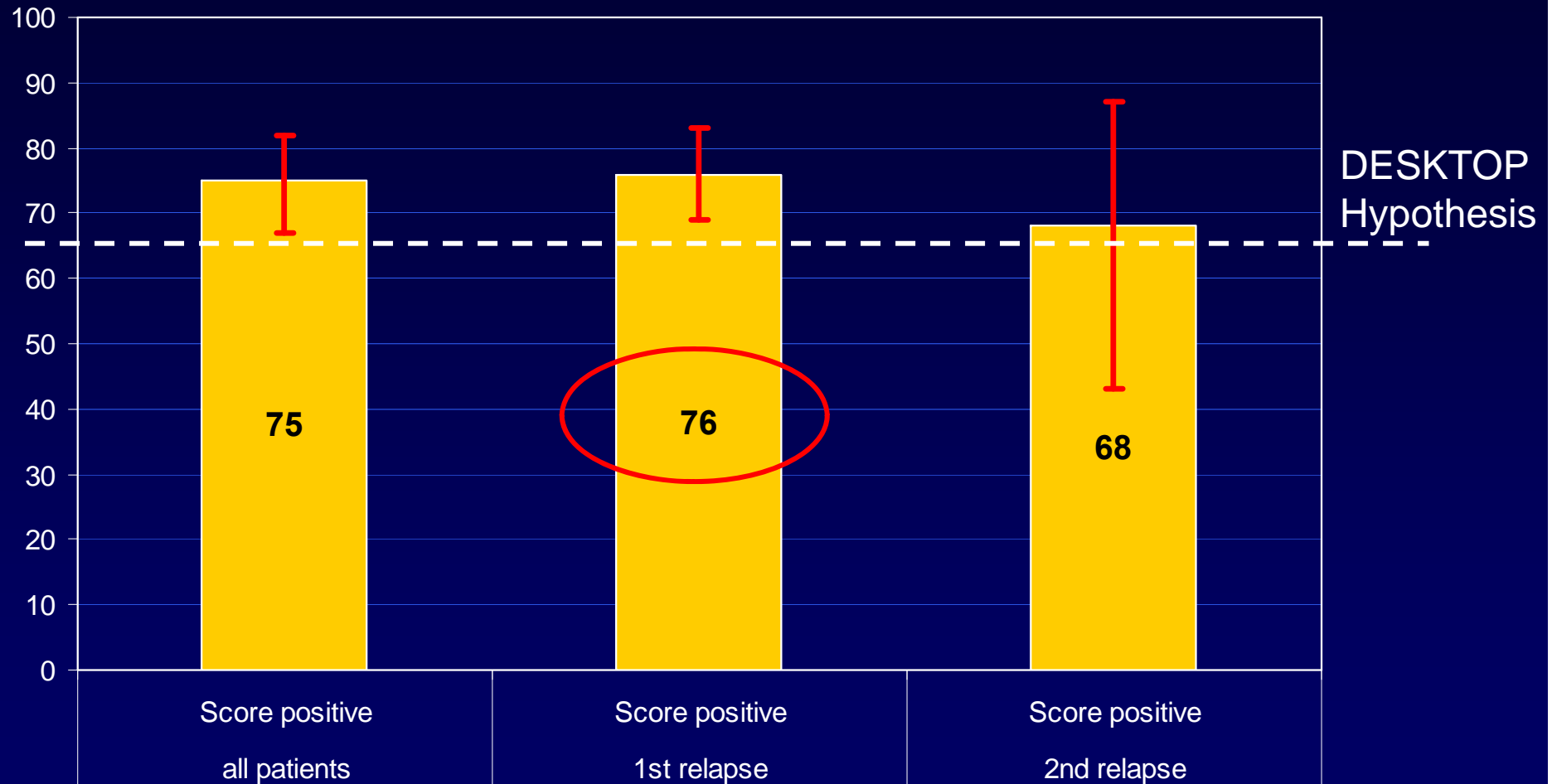
AGO DESKTOP OVAR II—Background

What Is The Surgical Endpoint?



AGO DESKTOP OVAR II—Surgical Results

Frequency of Complete Resection By Applying The AGO Score



Complete resection in 76% of the study collective =

AGO score could predict complete resection in at least 2 out of 3 patients

Harter P, et al. *Ann Surg Oncol*. 2006;13(12):1702-1710.

The Traditional Treatment Paradigm

Recurrence After First-Line Chemotherapy

**Platinum
Sensitive**

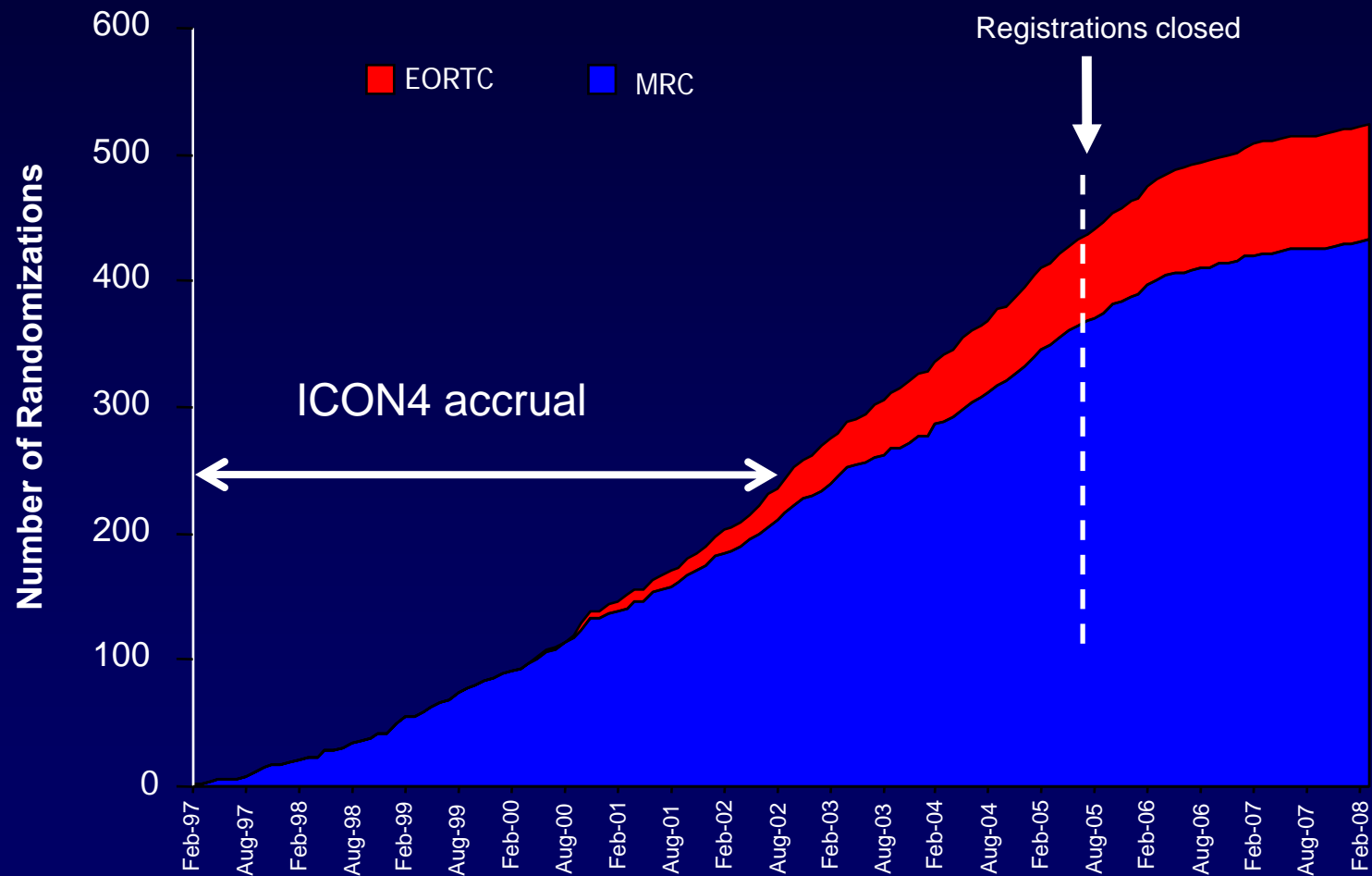


>6 Months



**Platinum
Retreatment**

Cumulative Randomizations



Second-Line Chemotherapy

Regimen Administered	Early N (%)	Delayed N (%)
Combination platinum	131 (49)	134 (51)
Combination platinum (no taxane)	40 (15)	33 (13)
Platinum + taxane-based	91 (34)	101 (38)
Carboplatin alone	78 (29)	67 (25)
Nonplatinum regimens	43 (17)	24 (9)
Taxane without platinum	15 (6)	9 (3)
Other	28 (11)	15 (6)
Absence of defined treatment	13 (5)	39 (15)
Unknown treatment	2 (1)	8 (3)
No treatment given	11 (4)	24 (9)
Not yet given (no clinical relapse)	0	7 (3)
Total	265	264

Trials of Combination vs Monotherapy in Platinum-Sensitive AOC

Author/ Group	Year	No. Pts	Regimens Evaluated	PFS	OS
Bolis ¹	2001	190	Carboplatin + Epirubicin vs Carboplatin	NS	NS
Cantù ²	2002	97	Cyclophosphamide + Doxorubicin + Cisplatin vs Paclitaxel	S	S
ICON IV ³	2003	802	Paclitaxel + Platinum vs Platinum	S	S
González- Martín GEICO ⁴	2005	81	Paclitaxel + Carboplatin vs Carboplatin	S	S
Pfisterer	2006	356	Carboplatin + Gemcitabine vs Carboplatin	S	NS

NS=not significant; S=significant;

1. Bolis G, et al. *Gynecol Oncol.* 2001;81(1):3-9. 2. Cantù MG, et al. *J Clin Oncol.* 2002;20(5):1232-1237. 3. Parmar MK, et al. *Lancet.* 2003;361(9375):2099-2106. 4. González-Martín AJ, et al. *Ann Oncol.* 2005;16(5):749-755. 5. Pfisterer J, et al. *J Clin Oncol.* 2006;24(29):4699-4707.

CALYPSO Trial

**Carboplatin & Pegylated
Liposomal Doxorubicin (PLD)
versus Carboplatin & Paclitaxel
in Relapsed, Platinum-Sensitive
Ovarian Cancer**

Eric Pujade-Lauraine

on behalf of all GCIIG collaborators

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



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

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

Key Eligibility Criteria

- Age ≥ 18 years
- ECOG performance status ≤ 2
- Histologically proven diagnosis of cancer of the ovary, fallopian tube, or extra-ovarian papillary serous tumors
- **Disease progression >6 months after first-line or second-line platinum-based therapy**
- Previous taxane exposure
- Measureable disease (RECIST criteria) or CA125 assessable disease (GCIg criteria) or histologically proven diagnosis of relapse

Endpoints. Statistical Discussions¹

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 trial²
- 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

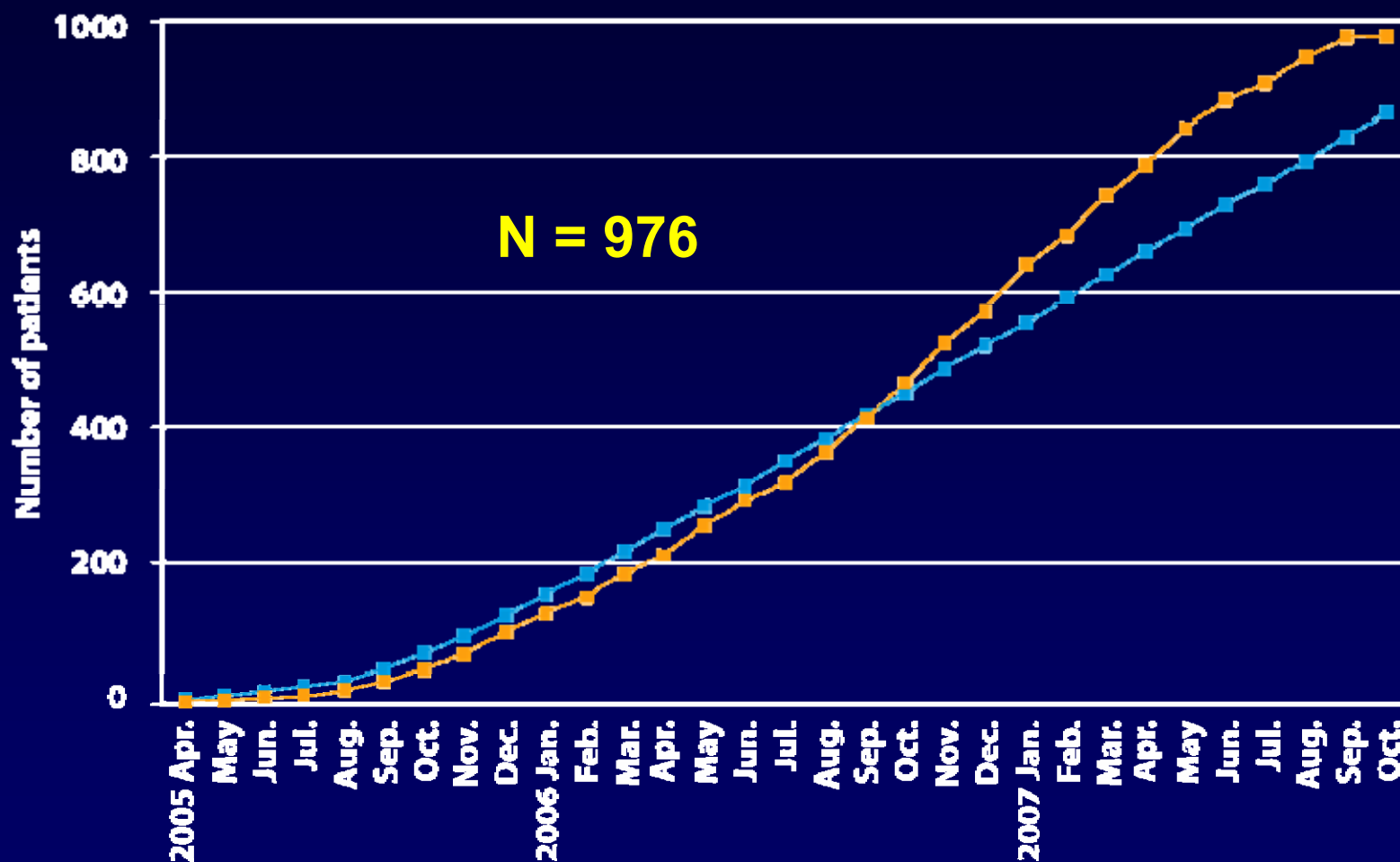
1. Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509. 2. Parmar MK, et al. *Lancet*. 2003;361(9375):2099-2106.

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



CALYPSO

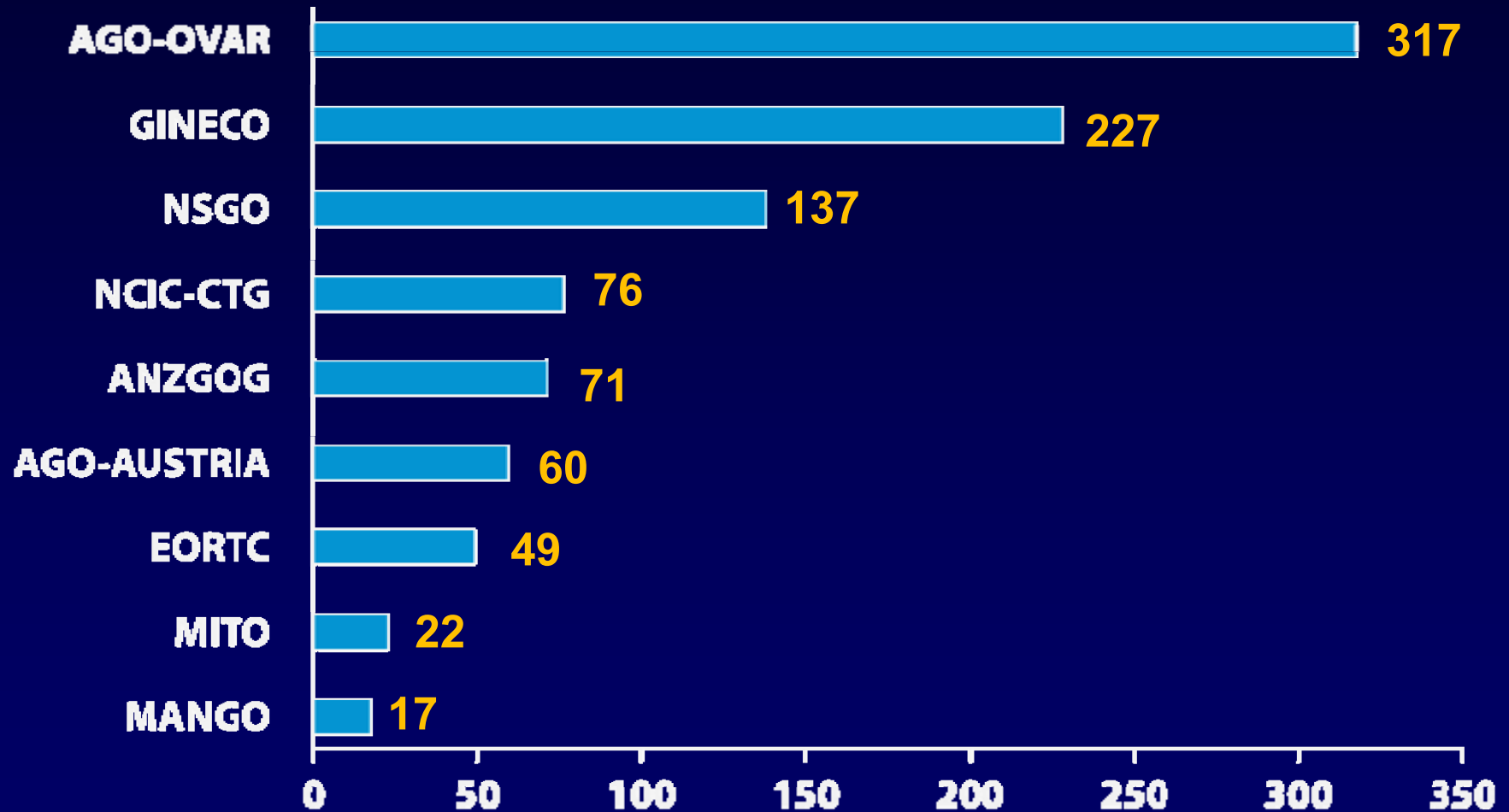
Worldwide Collaboration

Austria, Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, New Zealand, Norway, Saudi Arabia, Spain, Sweden, Switzerland, Turkey



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

Accrual by Groups



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)

Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509. #Missing values to attain 100%.

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)**
Total treatment duration, median week*	21	16
Relative dose intensity %	Carbo: 99 PLD: 99	Carbo: 99 Paclitaxel: 98
Patients with ≥ 6 cycles, n (%)*	395 (85)	392 (78)
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 (%)		
Neutropenia, grade 3	144 (31)	121 (24)	<.01
grade 4	20 (4)	108 (22)	
Febrile neutropenia, grade 3-4	10 (2)	21 (4)	NS
Infection, grade 3-4	11 (3)	14 (3)	NS
Thrombocytopenia, grade 3-4	73 (16)	31 (6)	<.01
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
Nausea/vomiting*	31%	4%	20%	4%
Constipation	19%	2%	20%	2%
Diarrhea	4%	2%	6%	2%
Arthralgia/myalgia*	4%	0%	18%	1%
Hand-foot syndrome*	11%	2%	2%	0%
Mucositis*	13%	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)
Alopecia grade 2*	7%	84%

P < .001

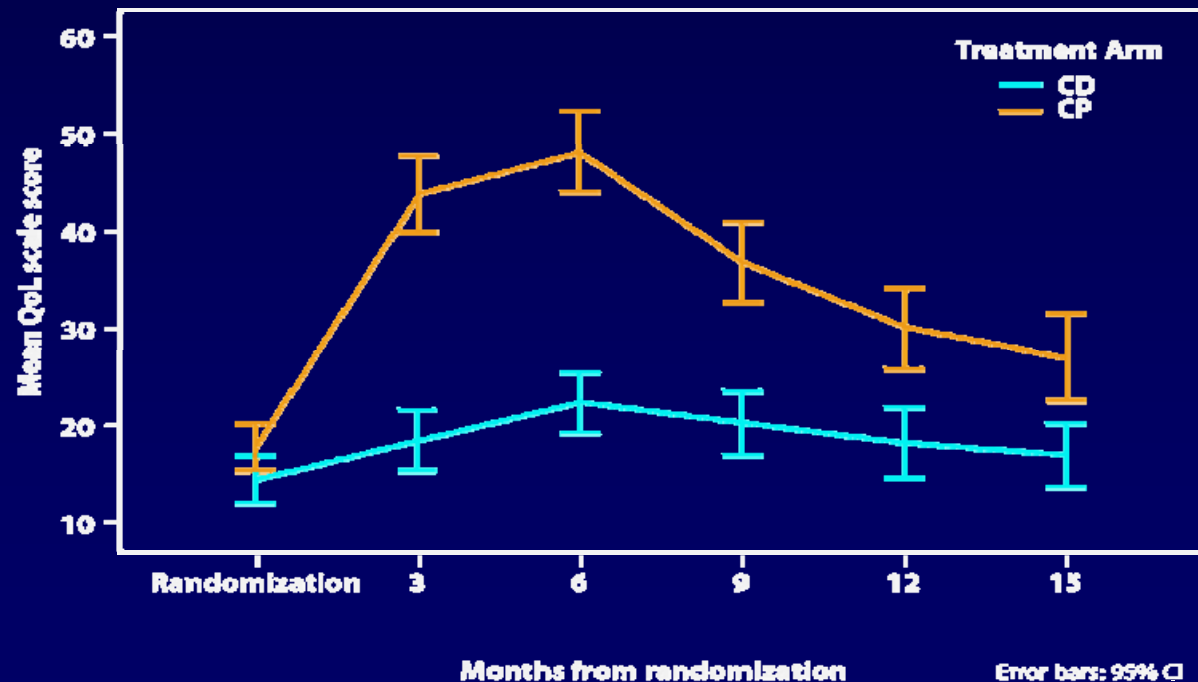
Long-Lasting Toxicity

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

* $P < .001$

EORTC OV28 – QoL Peripheral Neuropathy

Neuropathy score over time



Early Treatment Discontinuation

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

* $P < .001$

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%	

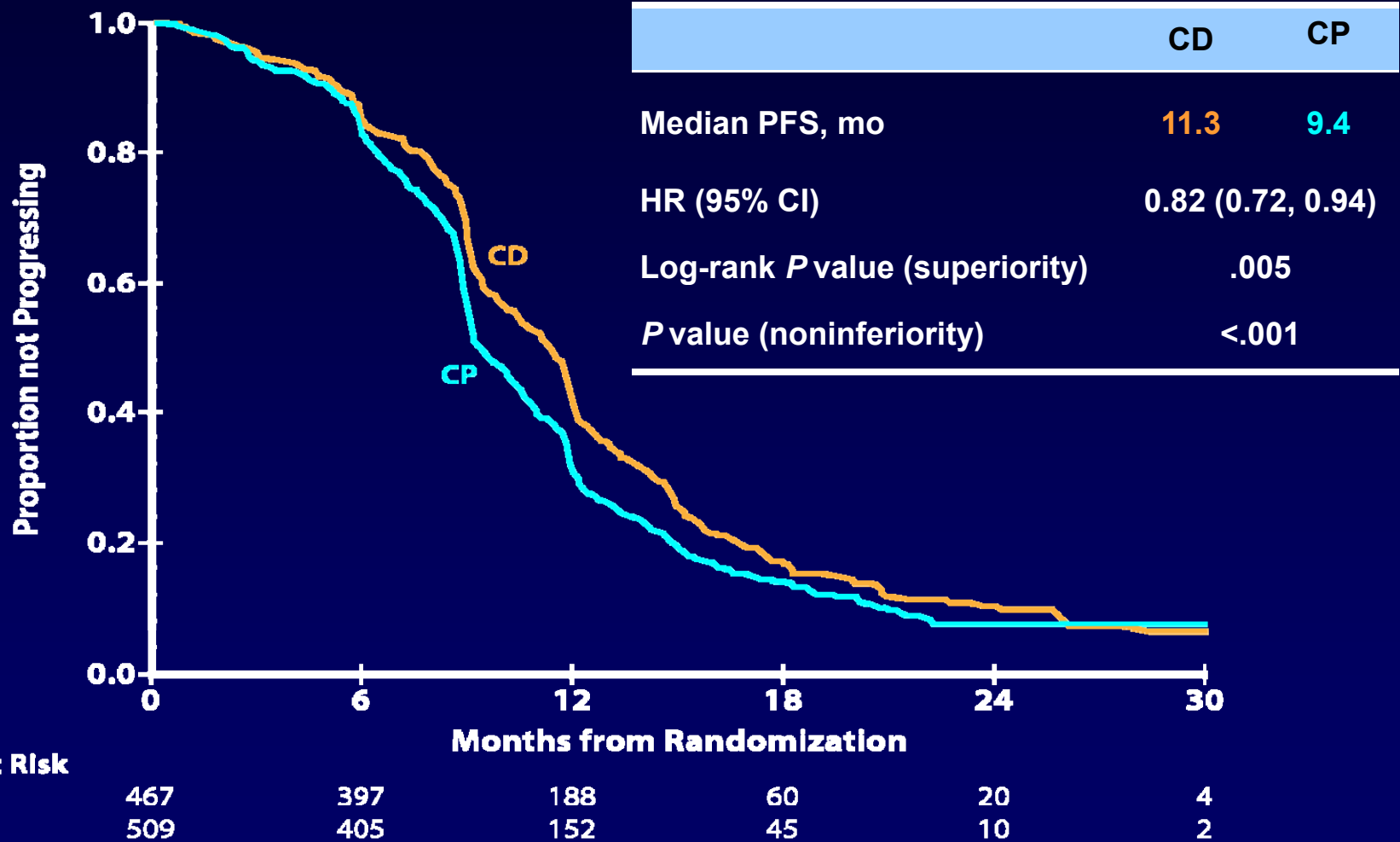
* $P < .001$

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

Follow-Up and Number of Events

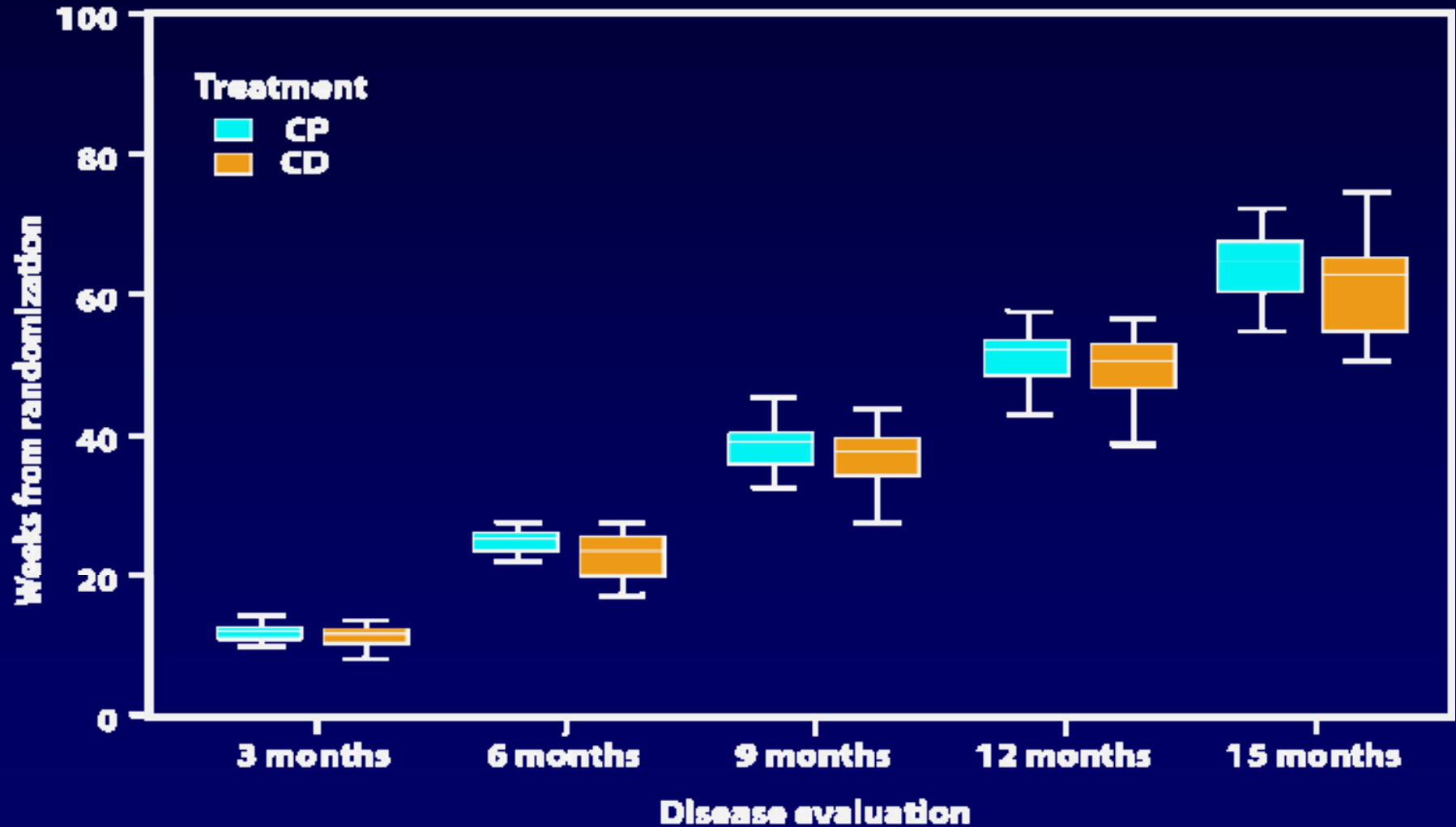
- **Median follow-up** **22 months**
- **Number of events**
 - **Progressions or deaths** **824 (85%)**
 - **Deaths** **322 (33%)**

Progression-Free Survival (ITT)



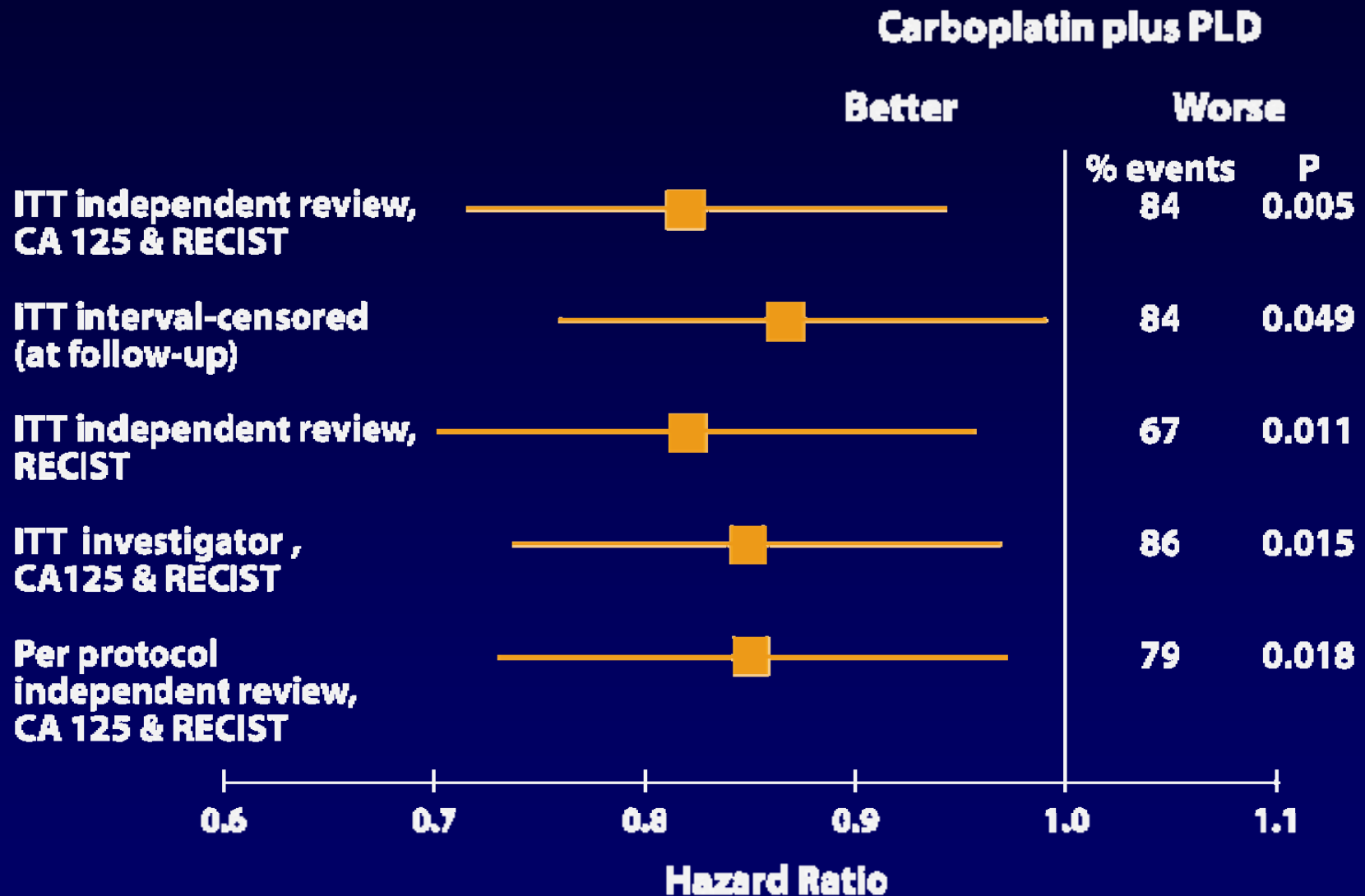
Pujade-Lauraine E, et al. *J Clin Oncol*. 2009;27(18S): Abstract LBA5509.

Symmetry of Tumor Assessments



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

Sensitivity PFS Analysis



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		

Key Findings

- 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; $P = .005$)
- Overall survival data immature, with only 322 deaths to date
- Paclitaxel-carboplatin associated with more severe toxicity (carboplatin hypersensitivity), alopecia, and long-lasting toxicity (neuropathy)
- Moderate reversible HFS, mucositis, and nausea/vomiting more frequent with PLD

Conclusions

- **Carboplatin-PLD demonstrated a superior therapeutic index (benefit/risk ratio) versus current standard, carboplatin-paclitaxel**
- **PLD-carboplatin offers an evidence-based option for patients with platinum-sensitive recurrent ovarian cancer**

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Patients and their families, and ...



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OVA 301 Trial: PLD vs PLD + Trabectedin

Summary of PFS Outcomes by Evaluation Method

N = 672	Median PFS, months		Hazard Ratio (<i>P</i> Value ^{**})
	PLD N = 335	T+ PLD N = 337	
All patients	5.8	7.3	0.80 (.0222)

* All randomized patients. Main OVA-301 analysis
pts with measurable disease: HR = 0.79, *P* value = .0190

** Log-rank test

Chemotherapy at Recurrence

Recurrence After First-Line Chemotherapy

