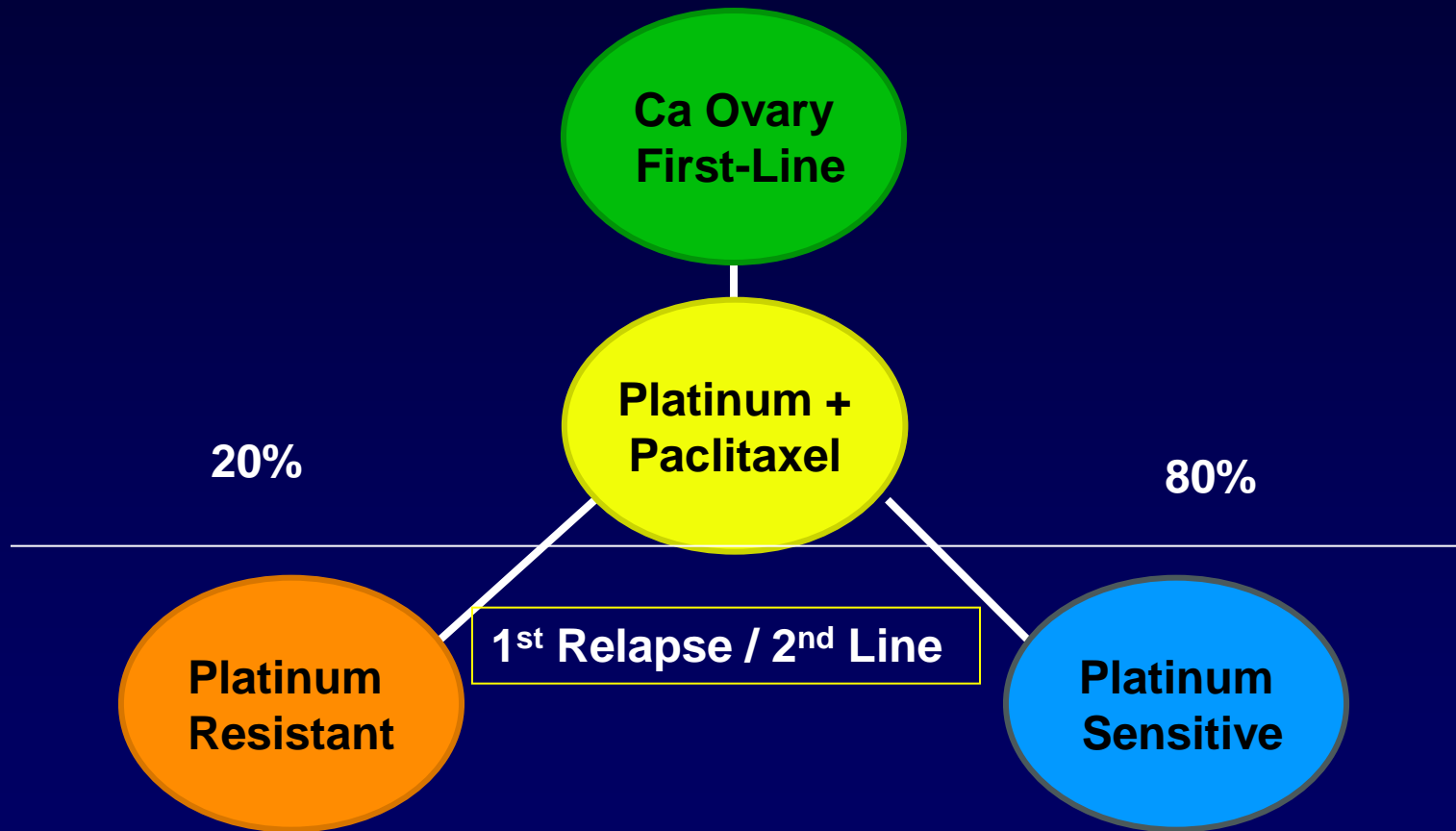


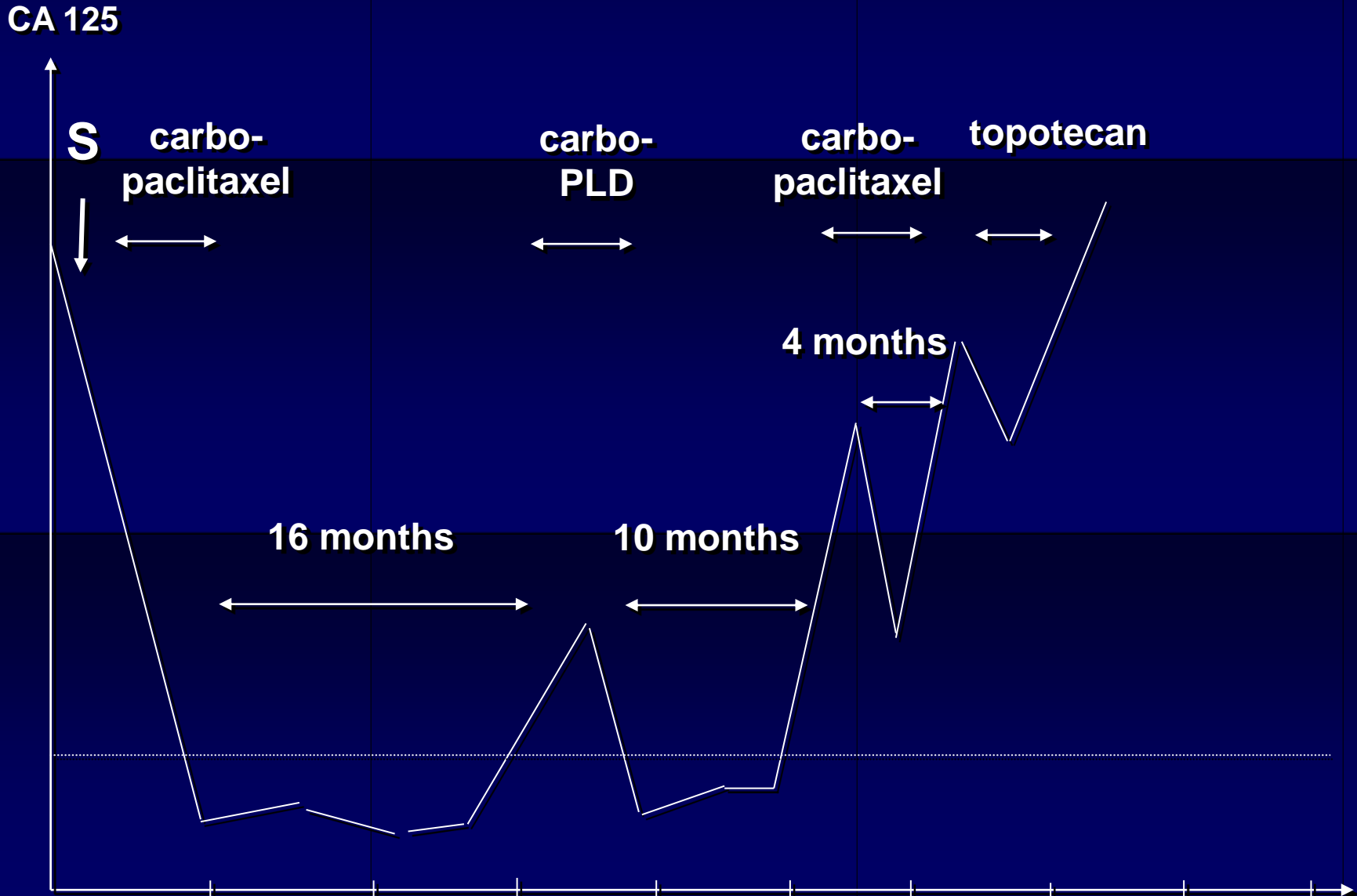
Case #5—Platinum-Resistant/Refractory Ovarian Carcinoma: Optimizing Quality of Life

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

Patient Segmentation Platinum Sensitivity



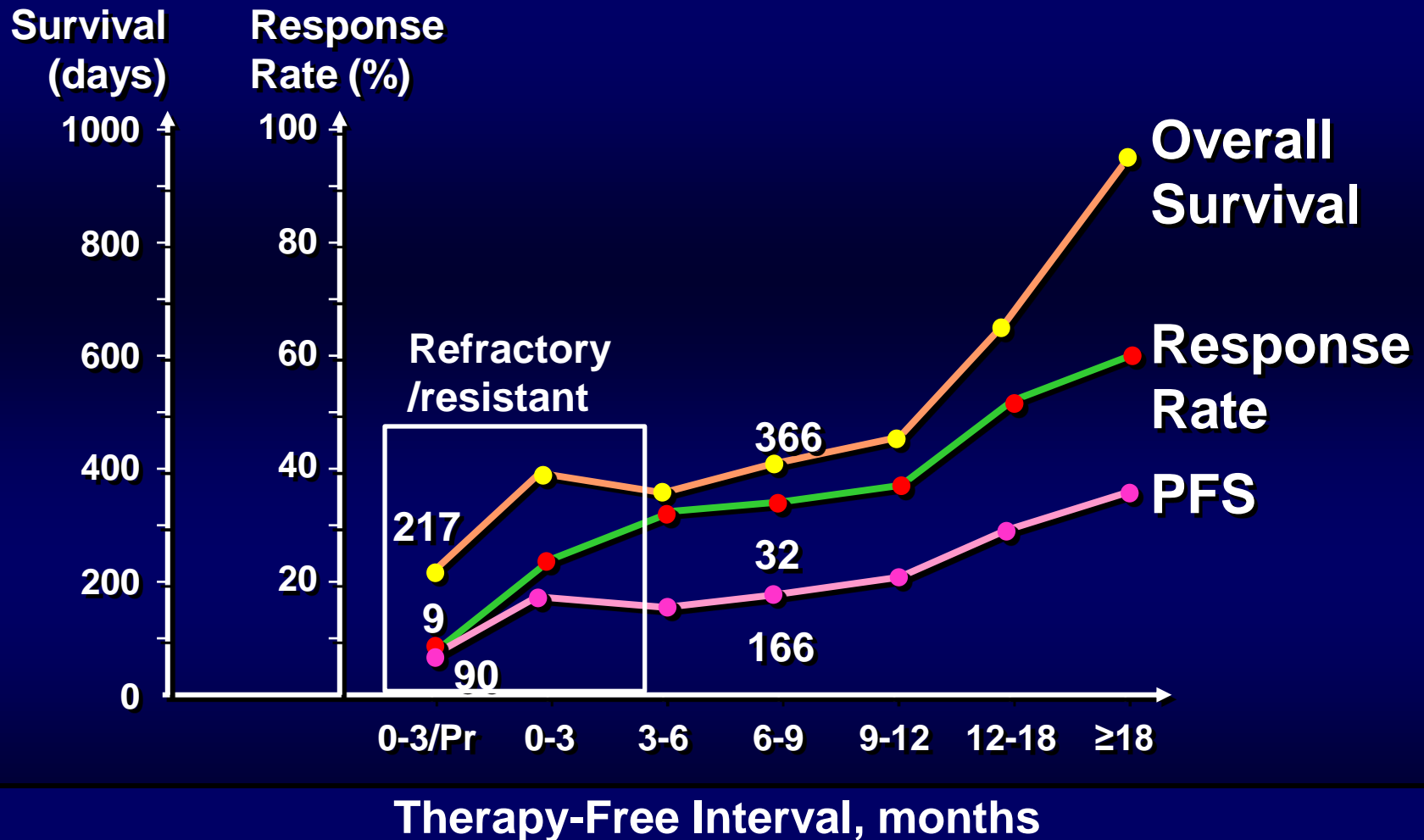
Advanced Ovarian Cancer: A “Chronic” Disease with Multiple Relapses



Factors to Consider in Choosing Treatment for Resistant ROC

- **What are the goals of treatment?**
- **Choice of treatment**
 - **Best option**
 - **Single agent**
 - **Single agent or combination**
- **Clinical trials**

A GINECO Study: Therapy-Free Interval and Efficacy



What Are Your Most Important Goals in the Treatment of Patients With ROC?

Gynecologist German Survey n = 327

Objective	Platinum-Resistant	Platinum-Sensitive
Quality of life	37.6%	19%
PFS	6.1%	15%
Survival	6.7%	22.6%

3rd International Ovarian Cancer Consensus Conference

3-5 September 2004, Black Forest, Germany

7-B3/2: Which *are* the recommended primary endpoints for future phase II and randomized phase III clinical trials in relapsing ovarian cancer?

- *Symptom control/quality of life (for **early** relapse) may be the preferred primary endpoints*

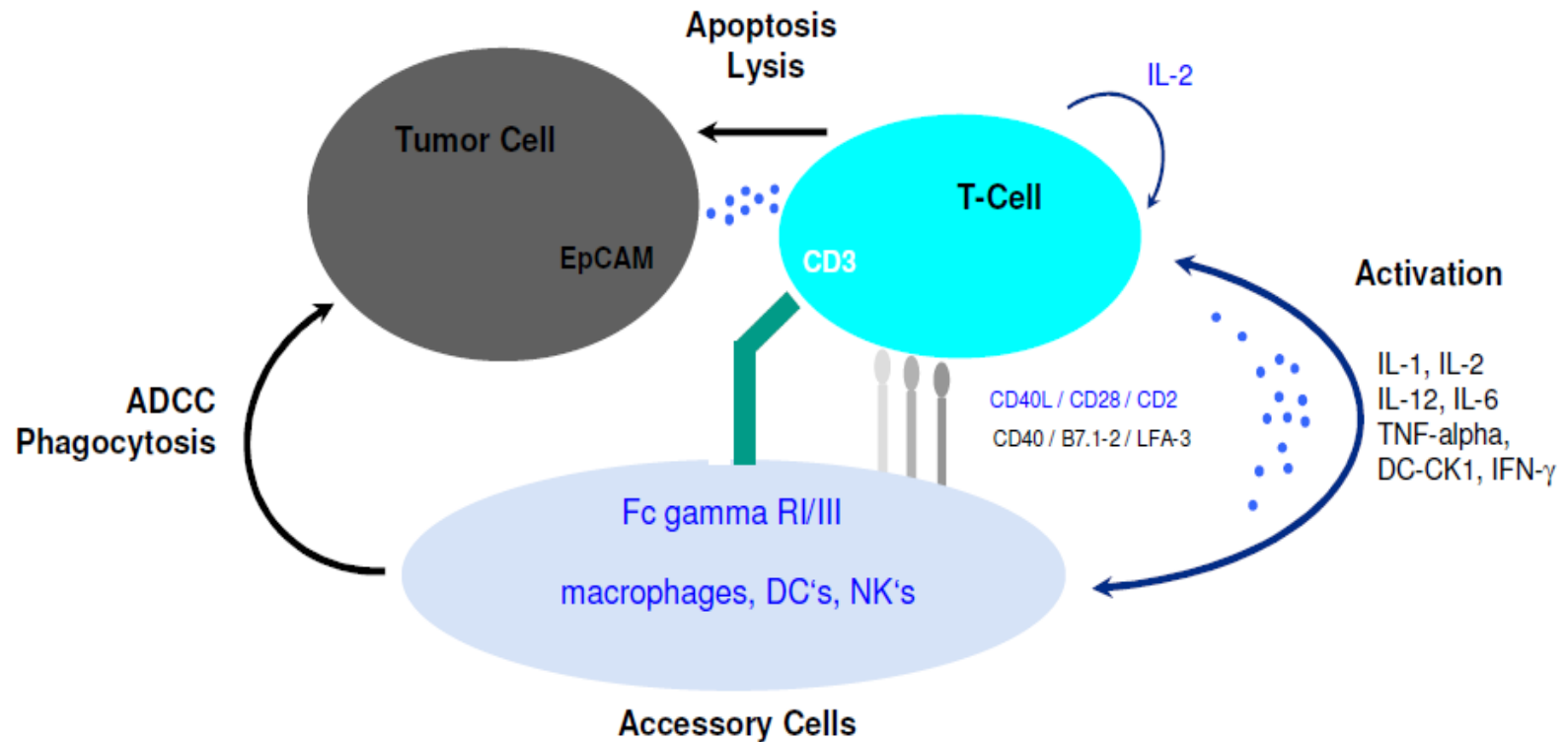
Factors to Consider in Choosing Treatment for Resistant ROC

- **What are the goals of treatment?**
- **Choice of treatment**
 - **Best options?**
 - **Single agent**
 - **Single agent or combination**
- **Clinical trials**

Best Options for Resistant Disease

- **Treat symptoms**
 - Ascite/pleural effusion drainage
 - Pain relief
 - Constipation alleviation
- **Enter the patient in a trial**

Trifunctional Antibody Catumaxomab (anti EpCAM x antiCD3)



The postulated Tri-cell-complex.

The intact trifunctional antibody catumaxomab accelerates the recognition and destruction of tumor cells by different immune cells. ADCC: Antibody dependent cellular toxicity; DC-CK1: Dendritic cell cytokine 1; IL: Interleukin; IFN- γ : Interferon gamma; LFA: Leukocyte function associated antigen; TNF-alpha: Tumor necrosis factor alpha.

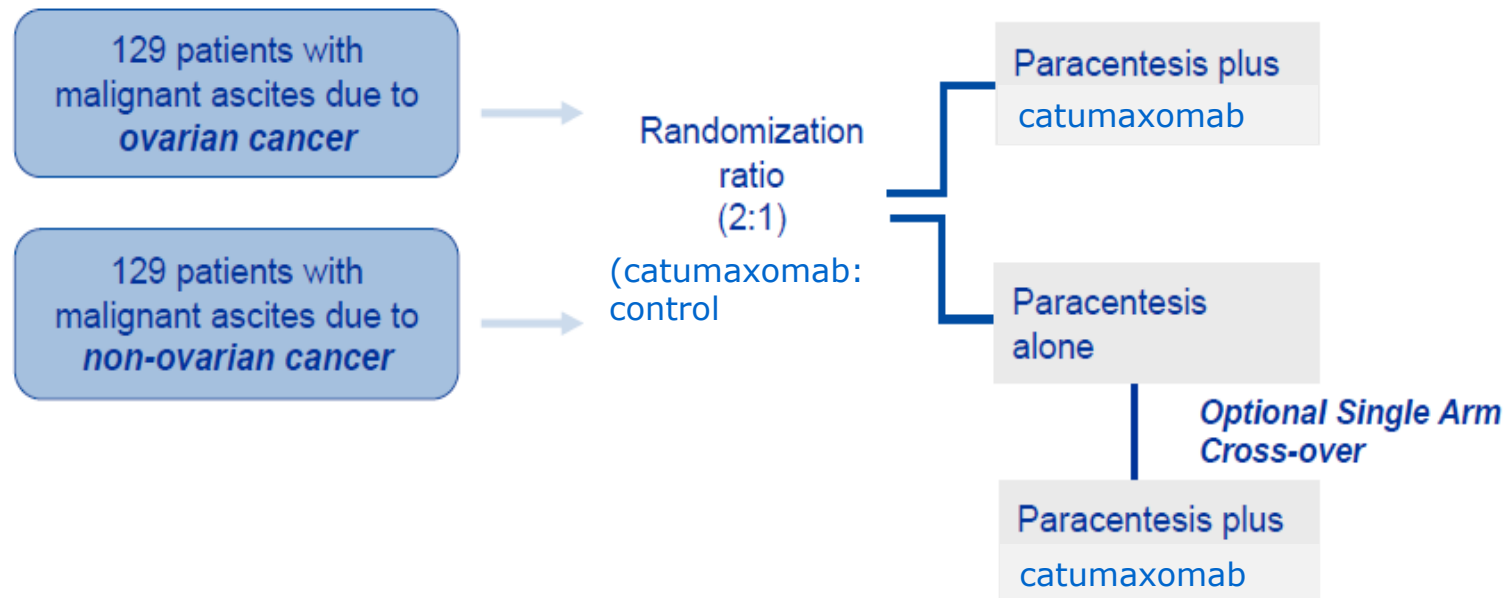
Catumaxomab

Trifunctional Antibody Targeting EpCAM

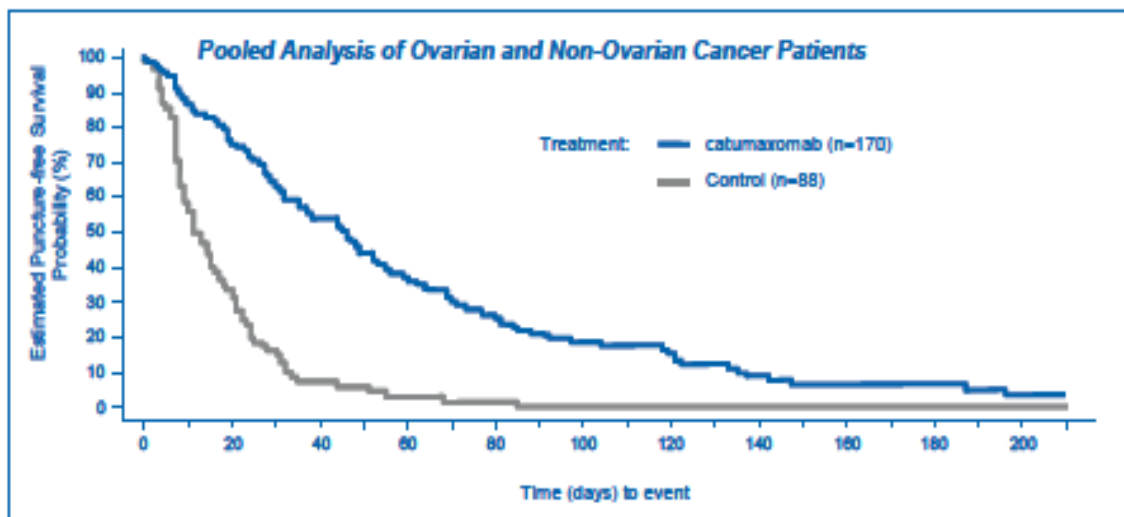
- Epithelial Cell Adhesion Molecule (EpCAM) is an appropriate target for intraperitoneal therapy
 - The vast majority of epithelial tumors express EpCAM
 - More than 90% of ovarian cancer and about 92% of gastric tumors express EpCAM
 - Cells of the peritoneum do not express EpCAM → tumor-specific targeting

Pivotal Study IP-REM-AC-01, phase II/III Study Design

- Two-arm, randomized, open-label study
- Two strata, independent sample size calculation (ovarian cancer, non-ovarian cancer)
- 4 i.p.-infusions at 10, 20, 50 and 150 μg of **catumaxomab on day 0, 3, 7 and 10**



Puncture-Free Survival (Primary Endpoint)



Median puncture free survival in days

	Pooled Population	Ovarian Cancer Stratum	Non-Ovarian Cancer Stratum	Gastric Cancer Subpopulation
Catumaxomab (Number of pat. with event)	46 (119)	52 (56)	37 (63)	44 (39)
Control (Number of pat. with event)	11 (82)	11 (42)	14 (40)	15 (18)
Difference [Factor]	35 [4.2]	41 [4.7]	23 [2.6]	29 [2.9]
P-value (log-rank test)	<0.0001	<0.0001	<0.0001	<0.0001

Factors to Consider in Choosing Treatment for Resistant ROC

- What are the goals of treatment?
- Choice of treatment
 - Best options
 - **Single agent?**
 - Single agent or combination
- **Clinical trials**

The Traditional Treatment Paradigm

Recurrence After First-Line Chemotherapy



Resistant Relapse

Chemoresistant Disease: Principles

- **Single-agent regimens**
- **Drugs active in resistant disease**
- **Treatment to progression, unacceptable toxicity with each regimen**
- **Sequential use of agents with goal of palliation and disease control**

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%

Ovarian Cancer Selecting Salvage Therapy



- **Disease control**
- **Favorable toxicity profile**
- **Convenience of administration**

Nonhematologic Toxicity of Nonplatinum Agents

Agent	Patient Tolerance/QoL Issues
Pegylated liposomal doxorubicin	HFS, mucositis
Paclitaxel	Alopecia, peripheral neuropathy, arthralgias/myalgias
Etoposide	Alopecia, GI toxicity
Gemcitabine	Flu-like constitutional symptoms, hepatic dysfunction, dyspnea
Docetaxel	Hypersensitivity, diarrhea, fluid retention
Vinorelbine	Constipation, nausea, peripheral neuropathy
Topotecan	Asthenia, alopecia, schedule

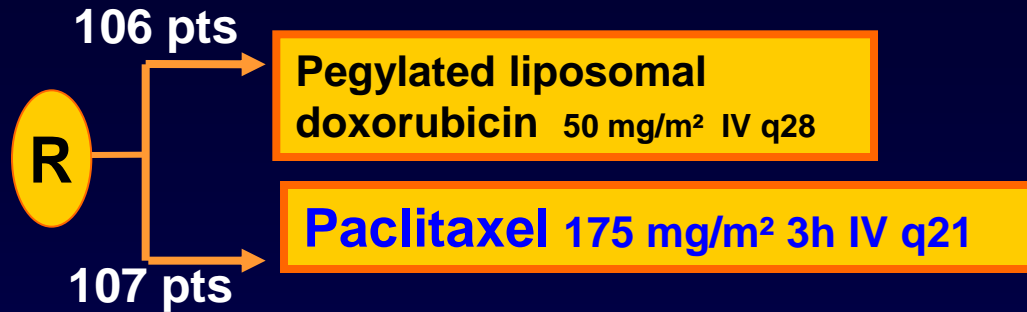
Resistant Relapse

Which Agent?

Pegylated liposomal doxorubicin first choice in platinum-resistant disease

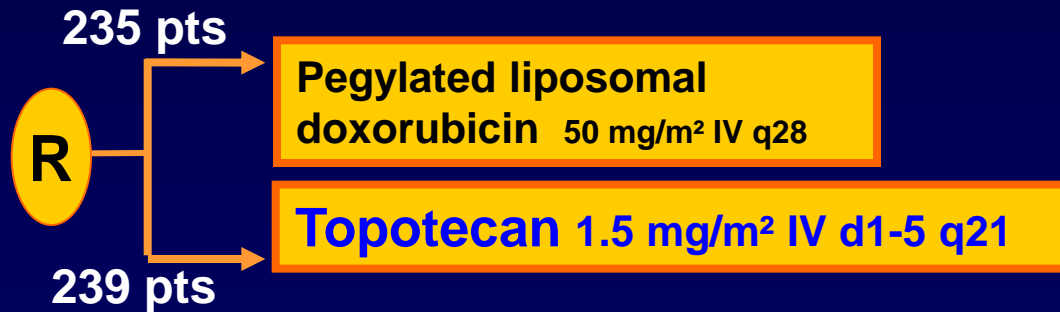
- One active agent not already used first-line and approved
- Toxicity profile bespeaks a very well-tolerated drug
- Convenience: Once every four weeks instead of weekly or daily times five

Pegylated Liposomal Doxorubicin (PLD) is Standard in Resistant OC



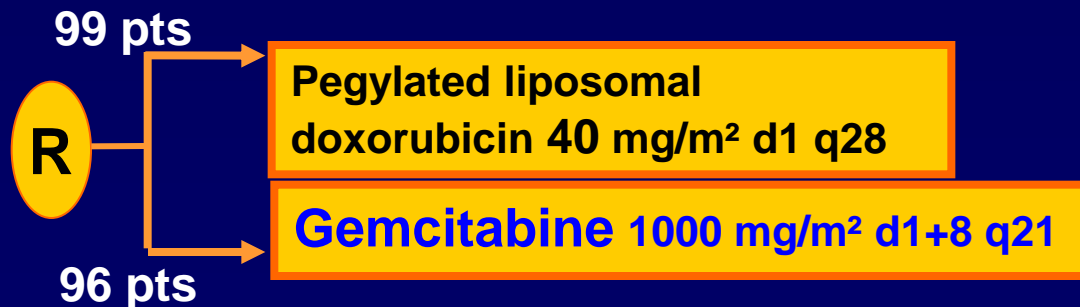
OR , median PFS and OS = similar. Cave: patients had no taxanes during first-line

O'Byrne KJ, et al. *Proc Am Soc Clin Oncol.* 2002;21: Abstract 808.



Median PFS = similar
Median OS = **PLD better**

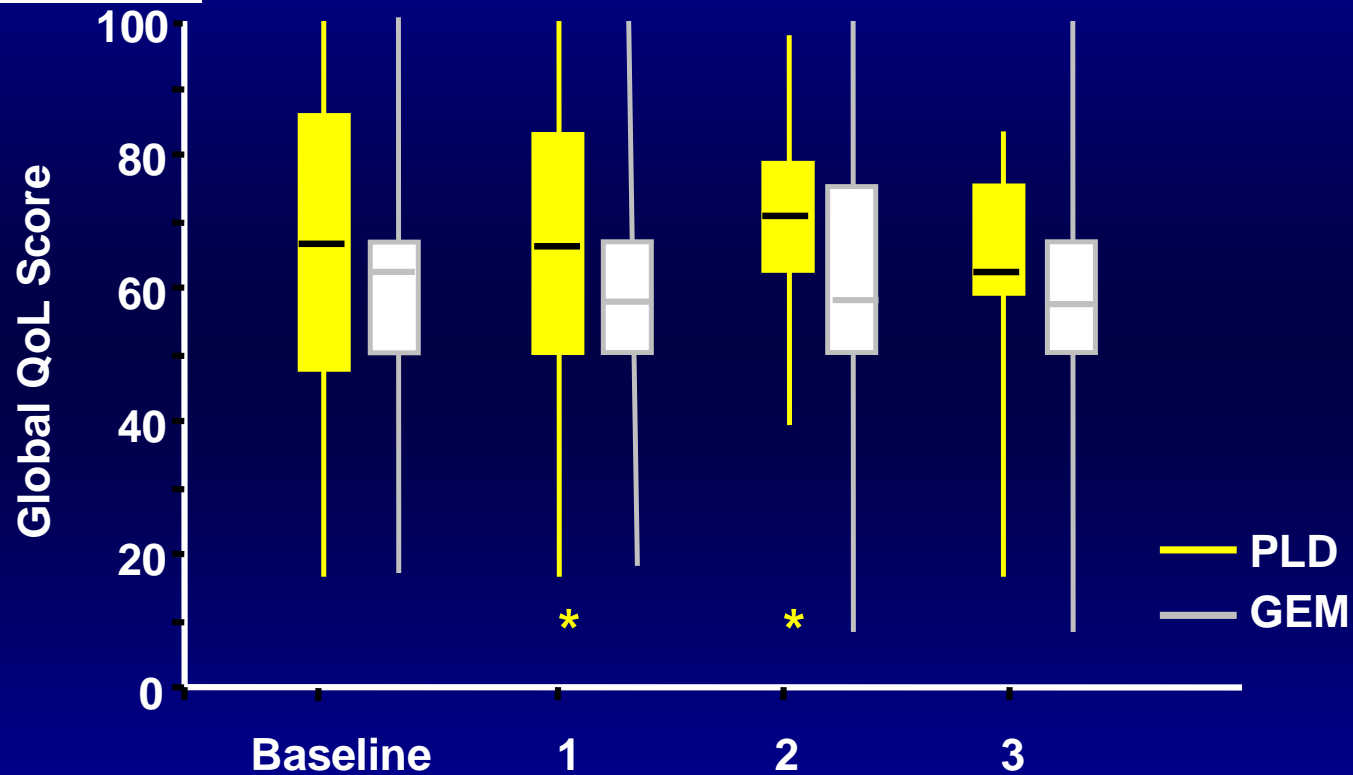
Gordon AN, et al. *Gynecol Oncol.* 2004;95(1):1-8.



Median PFS = similar
Median OS = **PLD better**

Mutch DG. *J Clin Oncol.* 2007;25(19):2811-2818

QoL Score According to Treatment Allocation

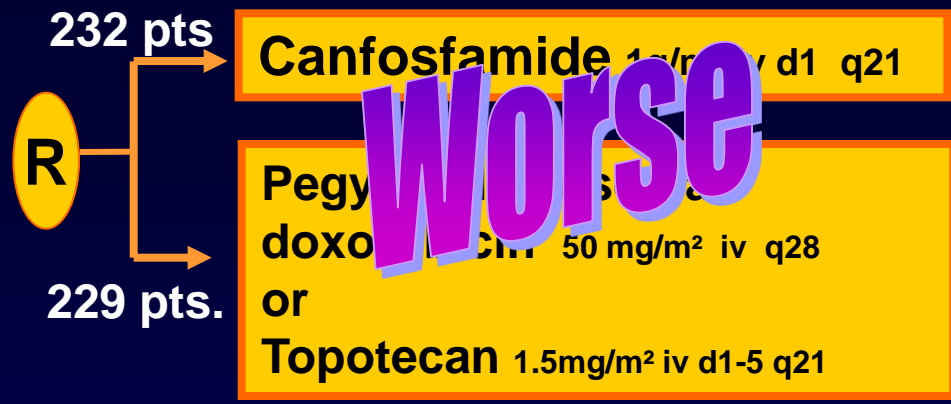


**P* value <.05

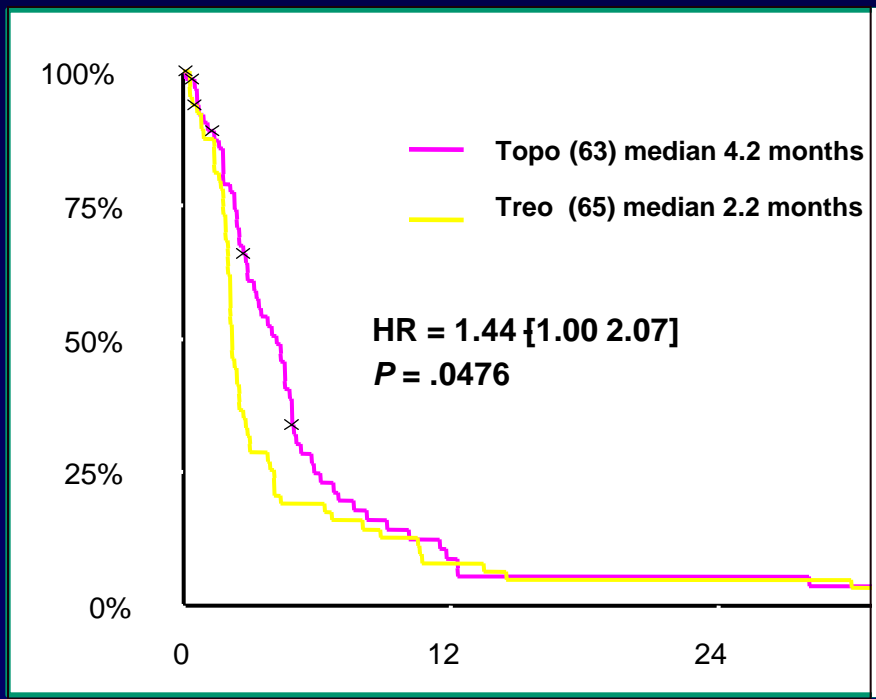


AGO-OVAR 2.3

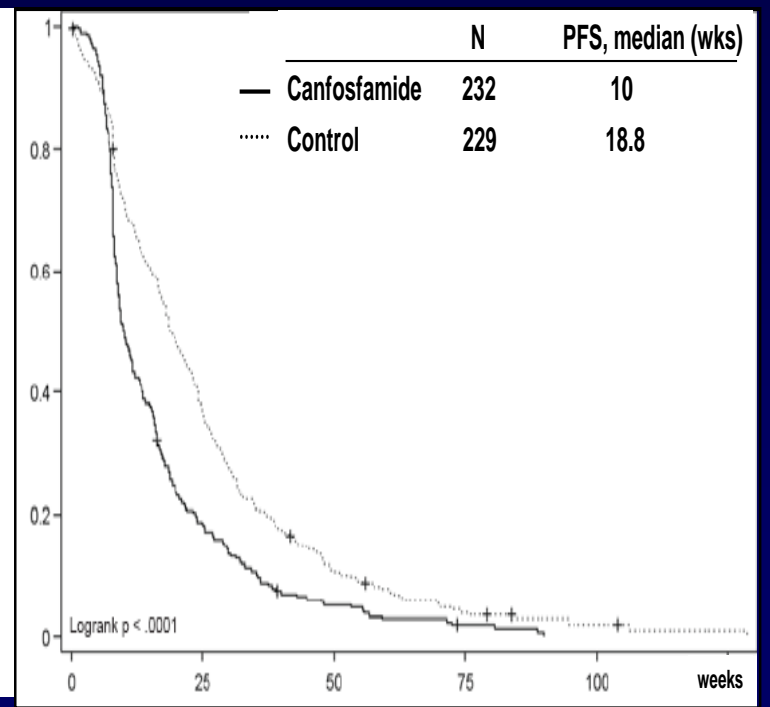
Meier W, et al. Proc Am Soc Clin Oncol. 2003;22: Abstract 1810.



Vergote I. Eur J Can. 2009;45:2324-2332.



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

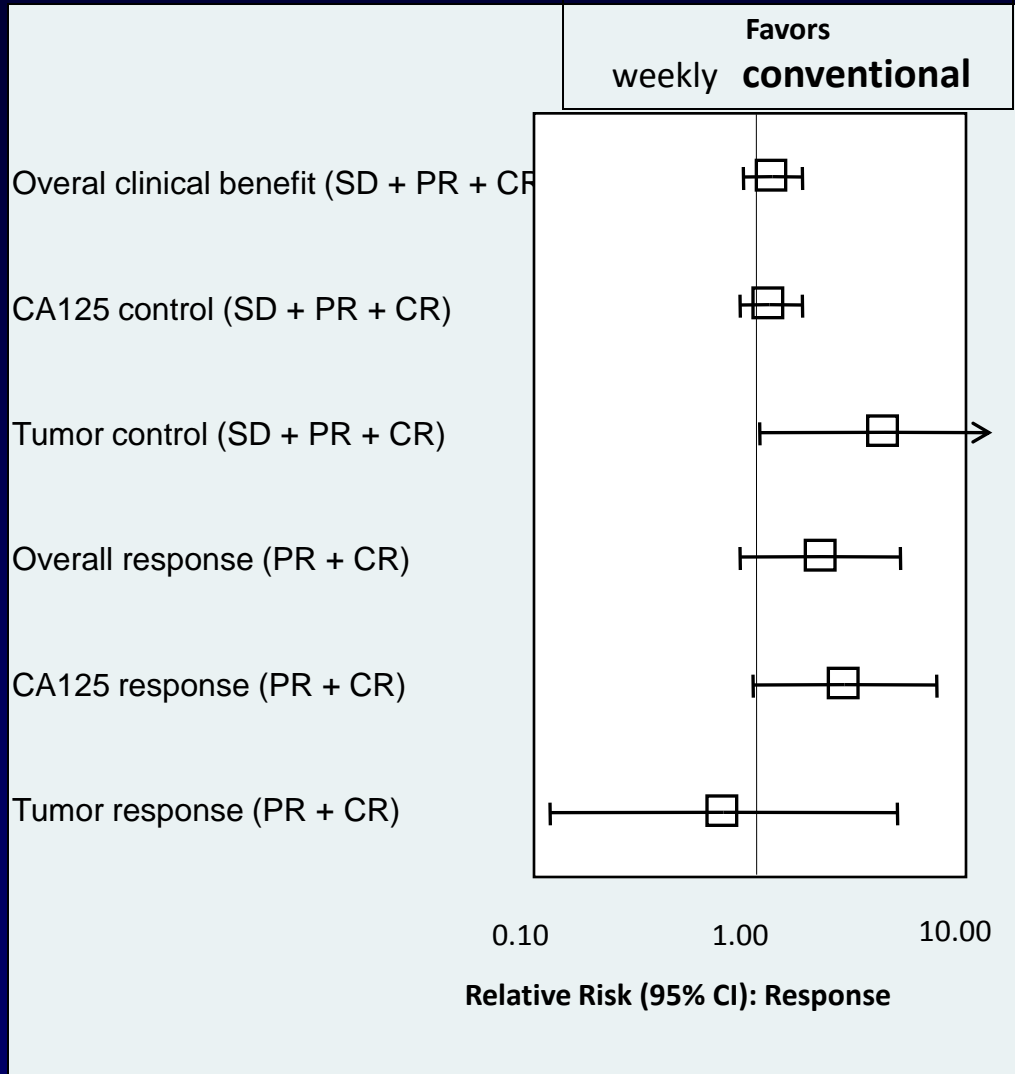


Topotecan Weekly (4 mg/m²/wk)
versus
Routine 5-Day Schedule (1.25 mg/m²/d x 5)
in Patients with Platinum-Resistant Ovarian
Cancer (TOWER):
A Randomized, Multicenter Trial of the
North-Eastern German Society of
Gynaecological Oncology (NOGGO)

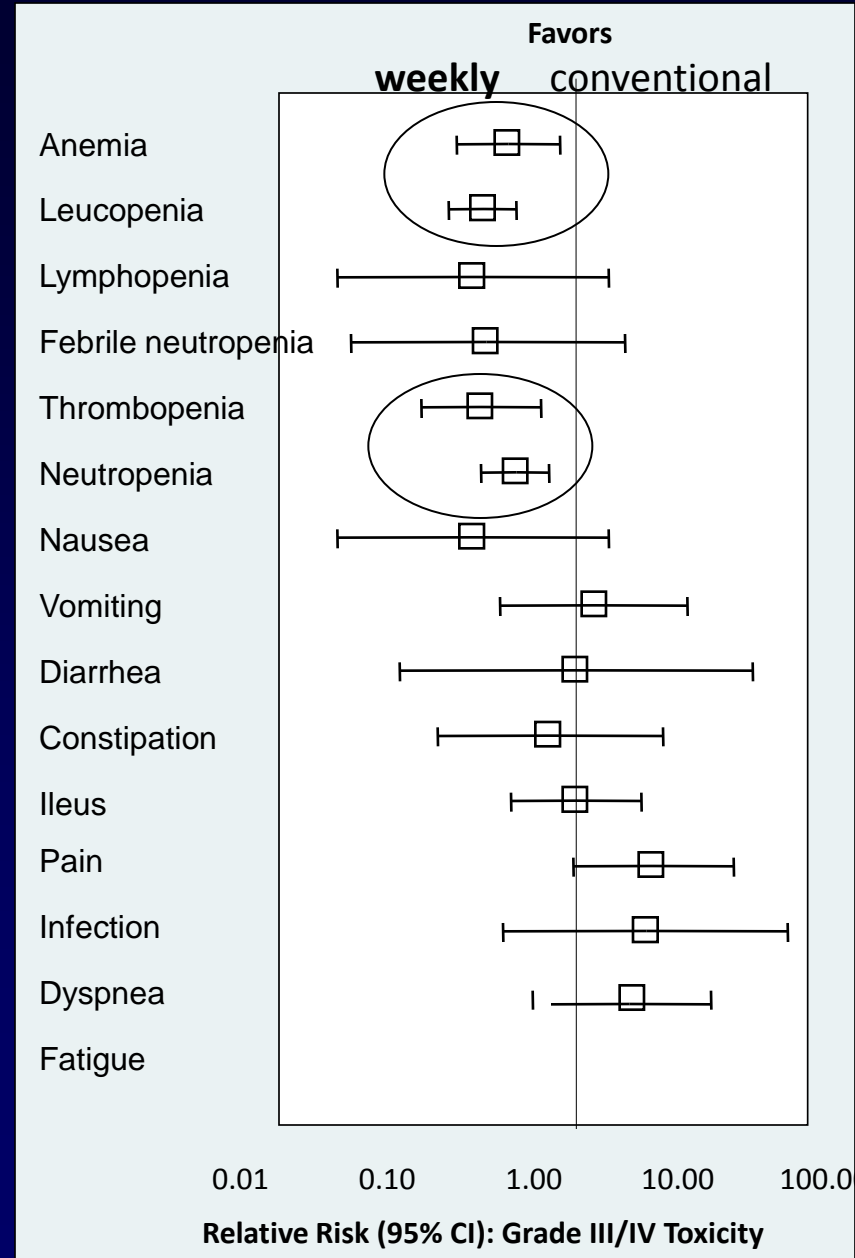
WWW.NOGGO.de

PI: Prof. Jalid Sehouli

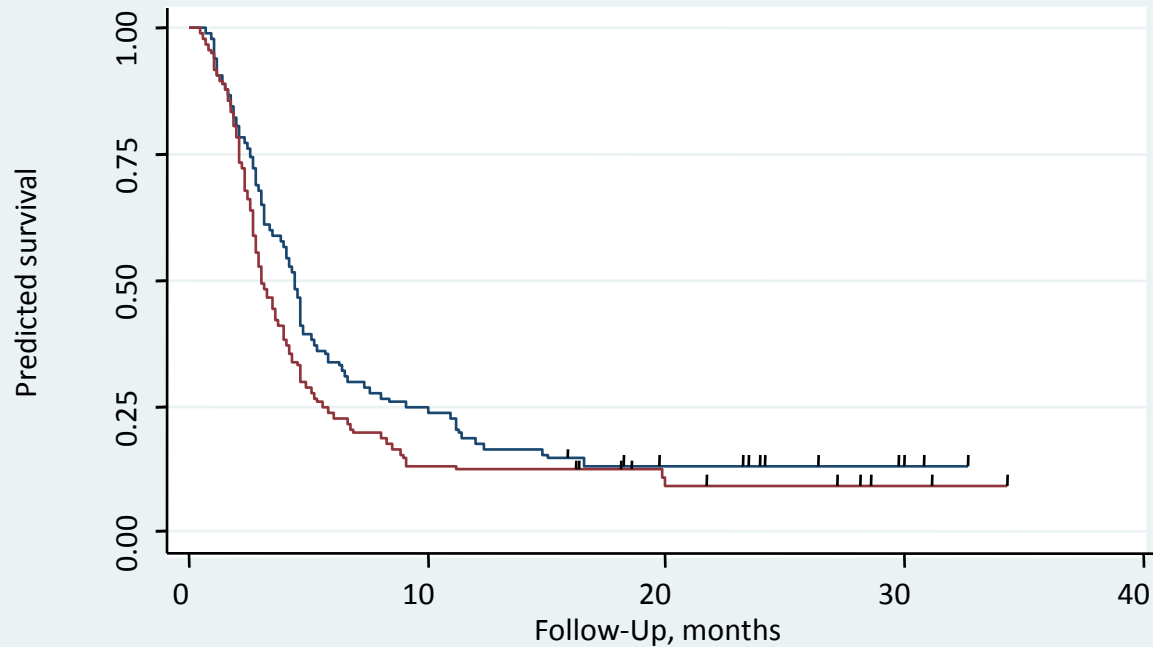
Responses by Subgroups



Toxicities



Progression-Free Survival

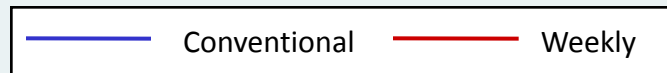


Number at risk

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), $P = .088$



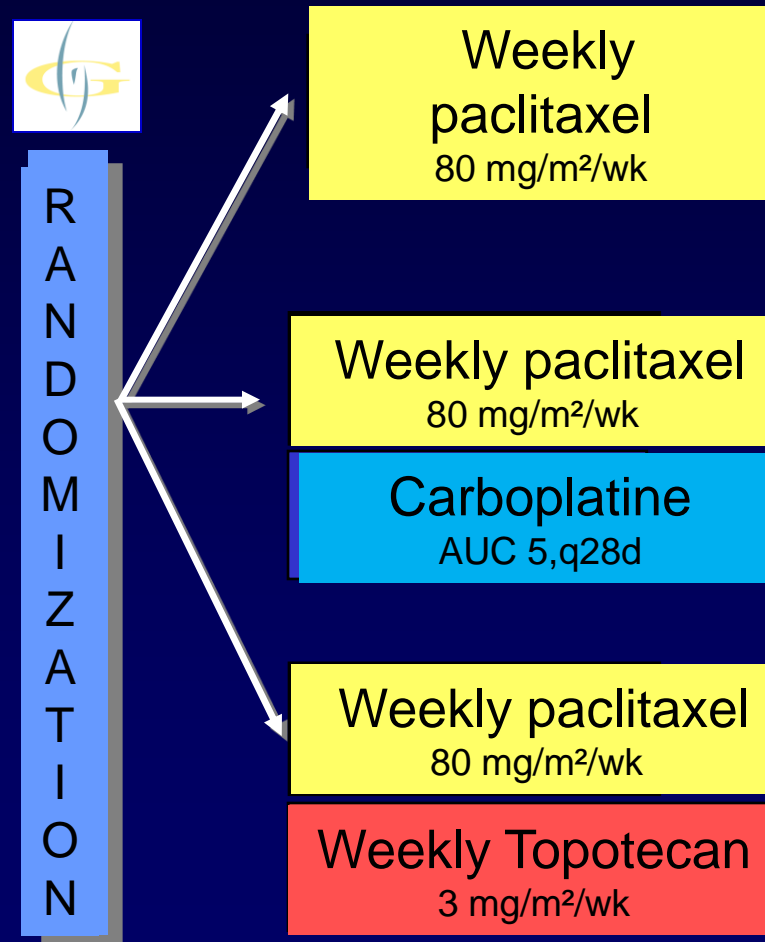
Predicted survival, months

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

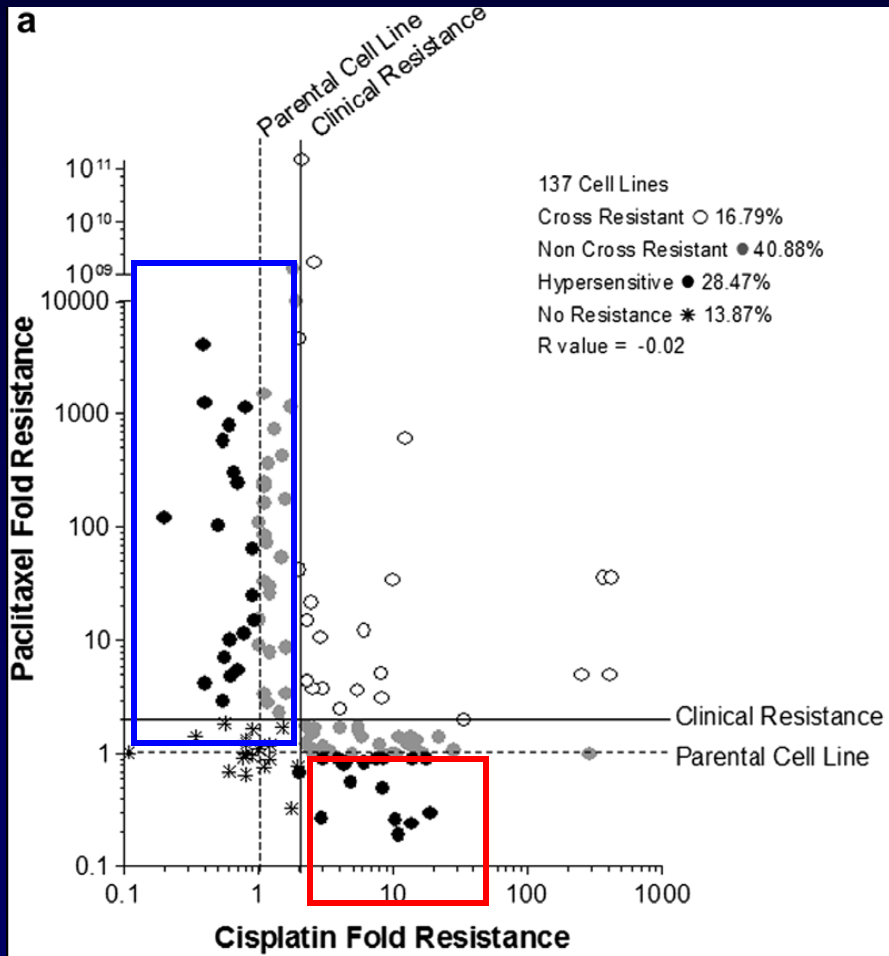
Factors to Consider in Choosing Treatment for Resistant ROC

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Resistant Relapse: Single Agent versus Doublets—GINECO Trial



Systematic Review of 137 Cell Models of Acquired Drug Resistance



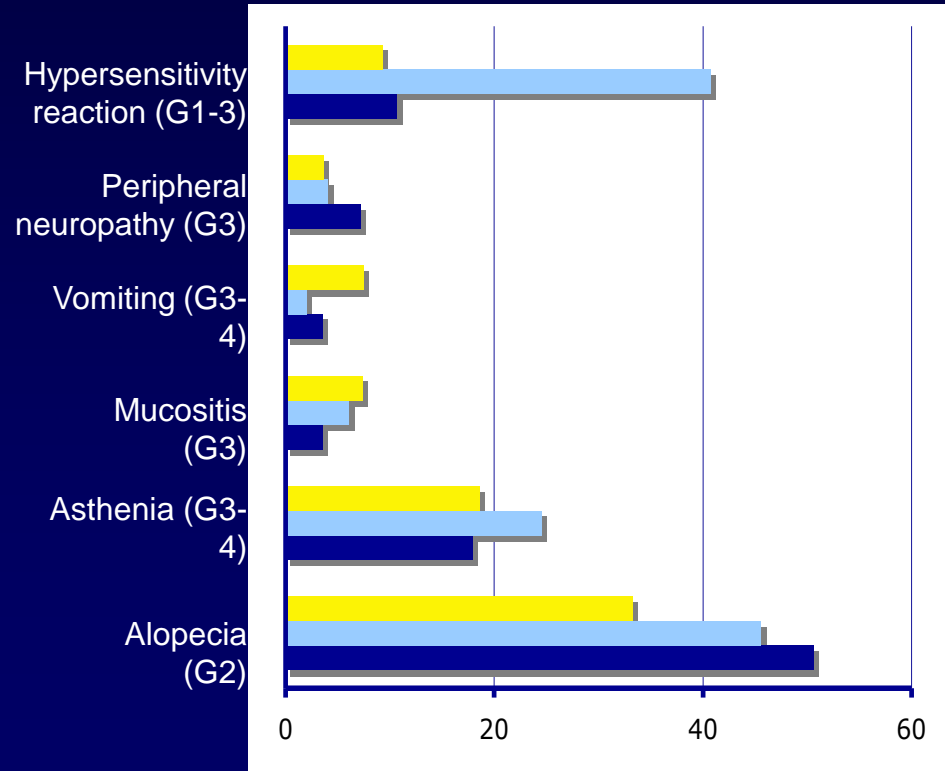
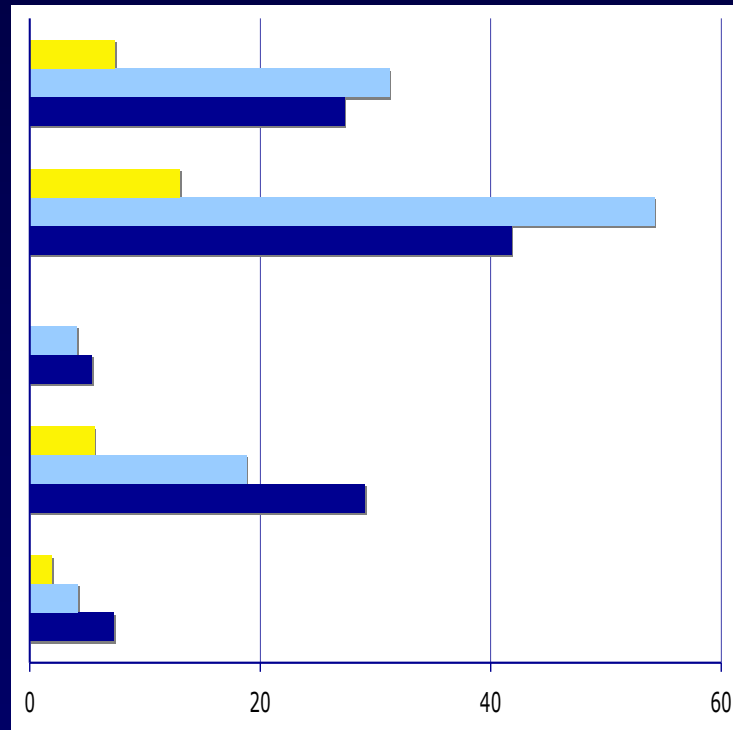
Inverse relationship between cisplatin and paclitaxel resistance in cell lines

Discontinuation From Drug Treatment For Toxicity

wP : 1.9 %
wP+C : 29.4 %
wP+wT : 22.8 %

Grade 3-4 hematologic toxicities

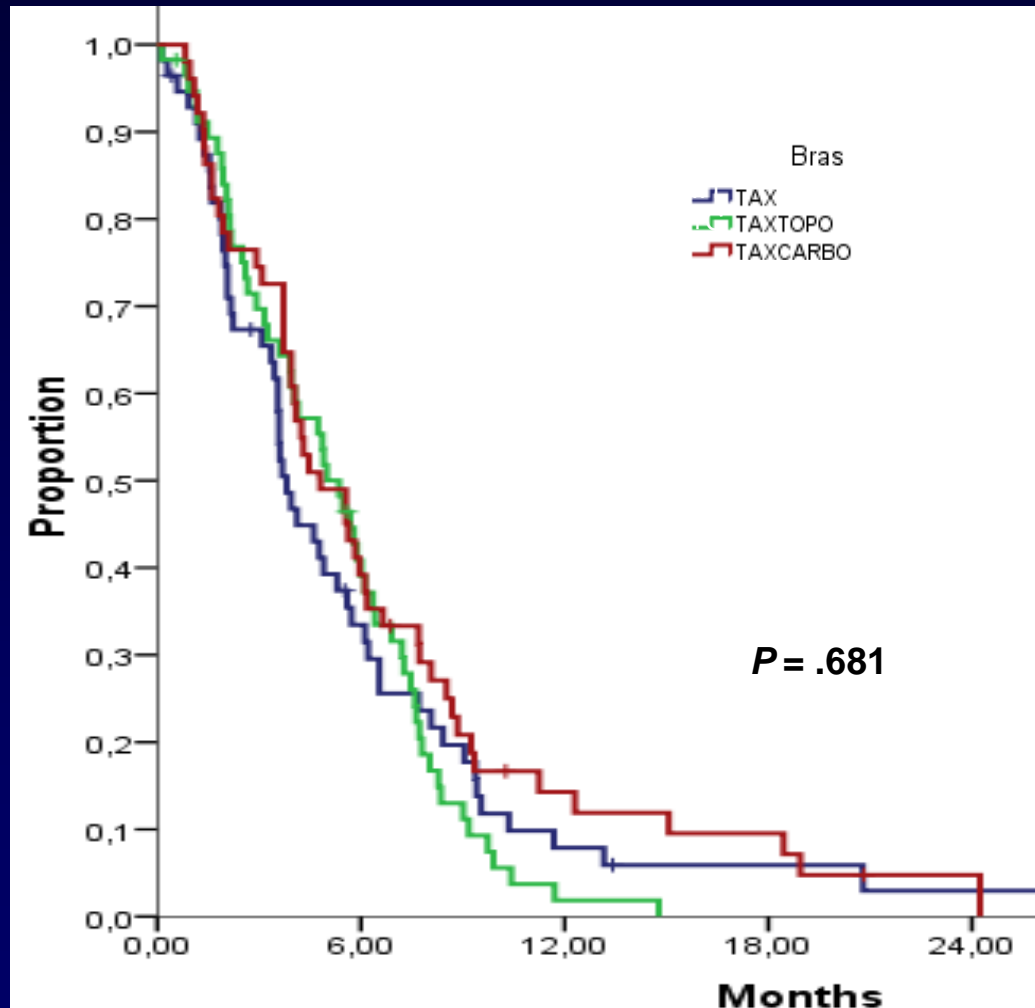
Nonhematologic toxicities



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

Single Agent versus Doublets— GINECO Trial—PFS Results



Randomized Trials of Single Agent Versus Combination In Resistant Disease

Regimens	Author	RR/PFS/OS Benefit
Paclitaxel vs epirubicin + paclitaxel	Bolis et al, 1999	No
Paclitaxel vs doxorubicin + paclitaxel	Torri et al, 2000	No
Paclitaxel vs epirubicin + paclitaxel	Buda et al, 2004	No
Topotecan vs topotecan + etoposide or gemcitabine	Sehouli et al, 2008	No
Pegylated liposomal doxorubicin vs PLD + trabectedin	Monk et al, 2008	No

Resistant Patients

- **Monotherapy remains standard**
- **Type of drug and schedule influence patient tolerance and outcome**

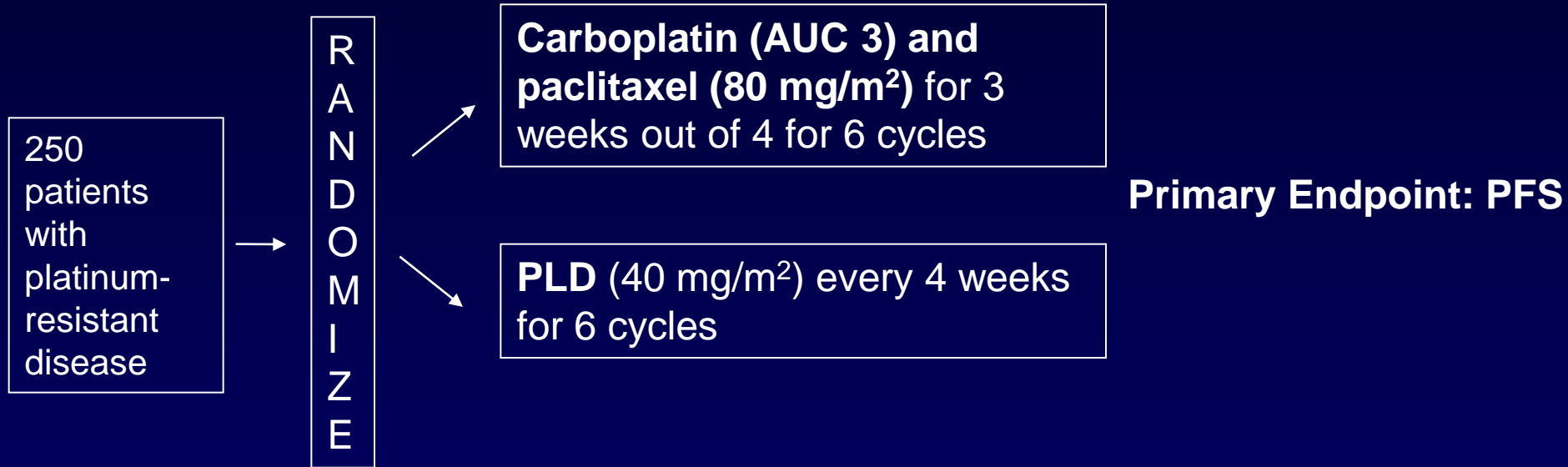
Factors to Consider in Choosing Treatment for Resistant ROC

- What are the goals of treatment?
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High RR and Long PFS in Series of Dose Dense/Fractionated Paclitaxel/Carboplatin Schedules

Regimen	RR %	PFS, months	OS, months	Ref
P90, Cb AUC4 Day 1 and 8 q21	43	6.75	8	Cadron 2007
P90, Cb AUC4 Day 1, 8, 15 q28 x2	53	10	13	Van der Burg 2004
P80, C AUC 2 Day 1, 8, 15 q28	37.5	3.2		Havrilesky 2003
P70, C AUC 3 Day 1, 8, 15 q 28	60	7.9	13.3	Sharma 2009

Scottish Trial of Dose-Dense Paclitaxel-Carboplatin Regimen in Resistant OC



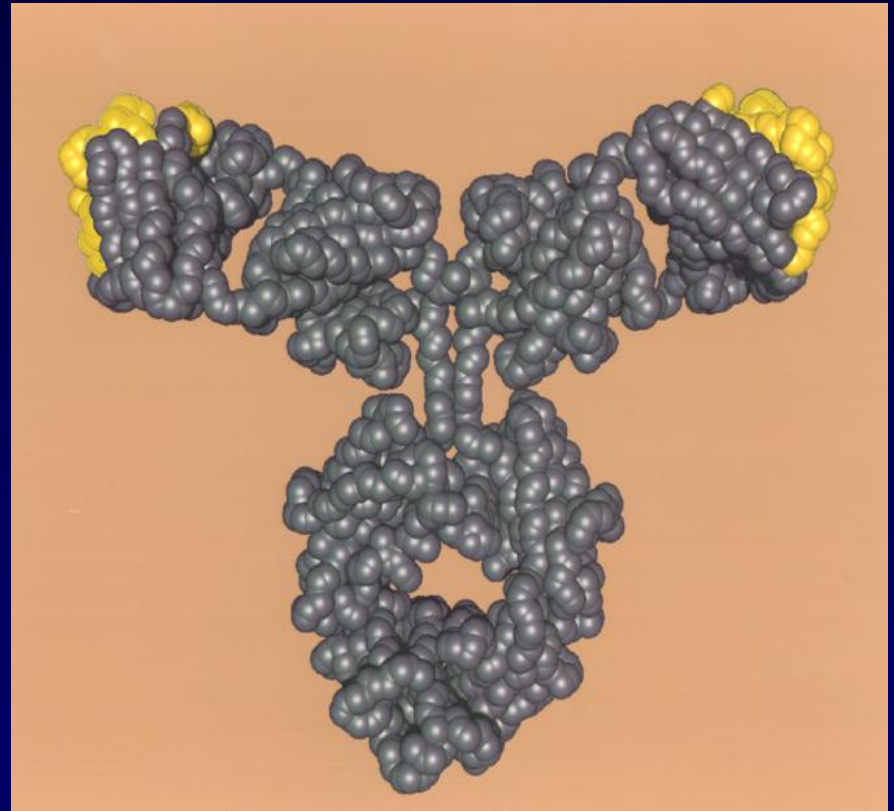
Secondary Endpoints:

- Overall Survival
- Quality of Life
- Health Economic Analysis
- Response Rate
- Toxicity/Hypersensitivity
- Dose Intensity
- Post progression therapy

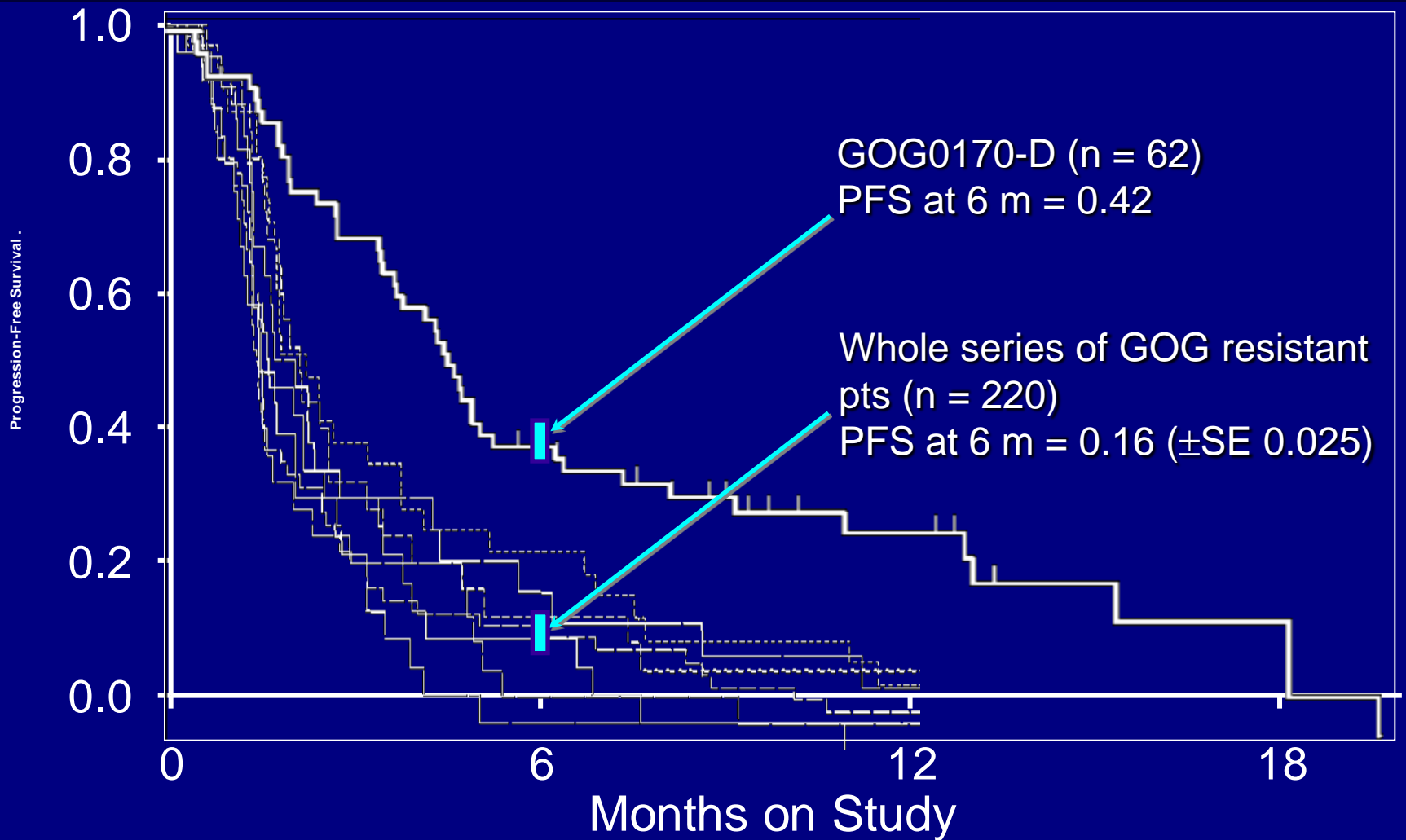


Unanswered Question

What is the role of bevacizumab in recurrent resistant ovarian cancer?

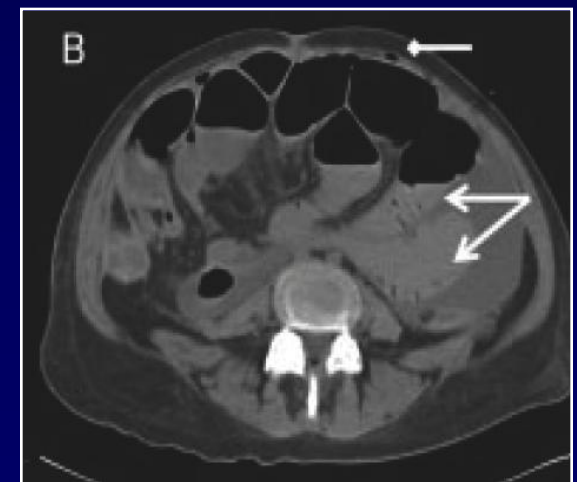


GOG0170D: Bevacizumab Phase II

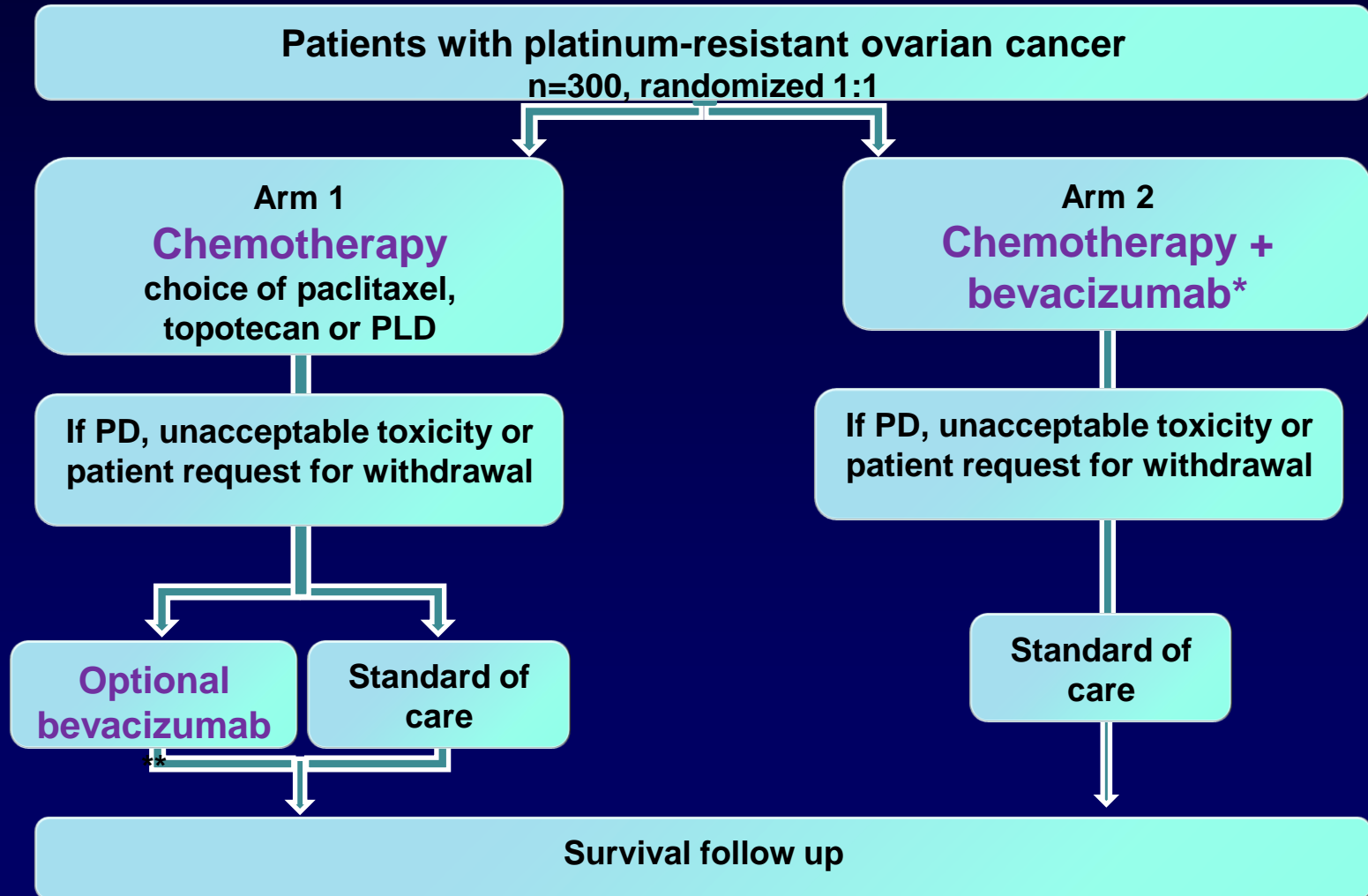


GI Perforations with Bevacizumab

Study	GIP
Burger (GOG-170D)	0/62
Garcia (ASCO 2005)	2/29
Cannistra (ASCO 2006)	5/44
Wright (ASCO 2006)	4/62
Friberg (ASCO 2006) -with erlotinib	2/13
Han (SGO 2006)	1/32
Total	14/181 (7.7%)



AURELIA: Avastin Use in REsistant ovarian epitheLIAI cancer



*10 mg/kg IV q2w (15 mg/kg q3w will be used instead if topotecan is selected and administered at a dose of 1.25 mg/m² on a 1–5/q3w schedule); ** 15 mg/kg i.v. q3w; PLD, Pegylated liposomal doxorubicin; PD, progressive disease

Issues

Quality of life is a key determinant

GCIIG Symptom Benefit Working Group

Issues

- ✓ **What symptoms are most important to patients?**
- ✓ **How these symptoms are related to clinical outcome?**

GCIIG Symptom Benefit Working Group

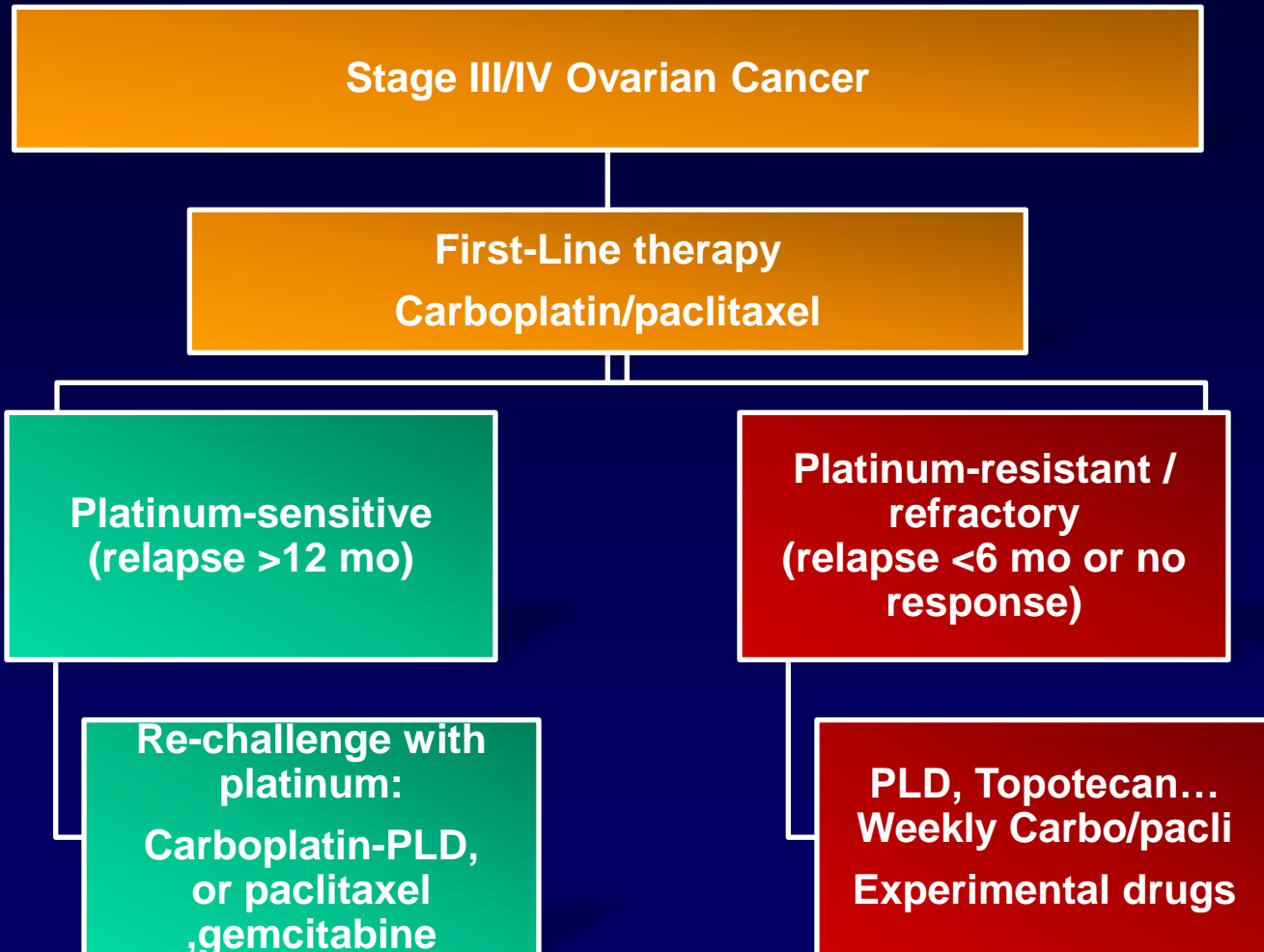
Methods: Survey in patients with ovarian cancer in relapse

- ✓ **Checklist of predefined symptoms:
Grading of severity and personal impact**
- ✓ **Additional question: What are the 3 most
bothering symptoms to you?**

Issues in developing symptom index

- ✓ One composite index or multiple measures of individual symptoms (eg, fatigue, pain, GI symptoms, psychological symptoms)?

Treatment Algorithm



Adapted from the NICE Guidelines.