

# PLATINUM- REFRACTORY/RESISTANT OVARIAN CANCER: Optimizing Quality of Life

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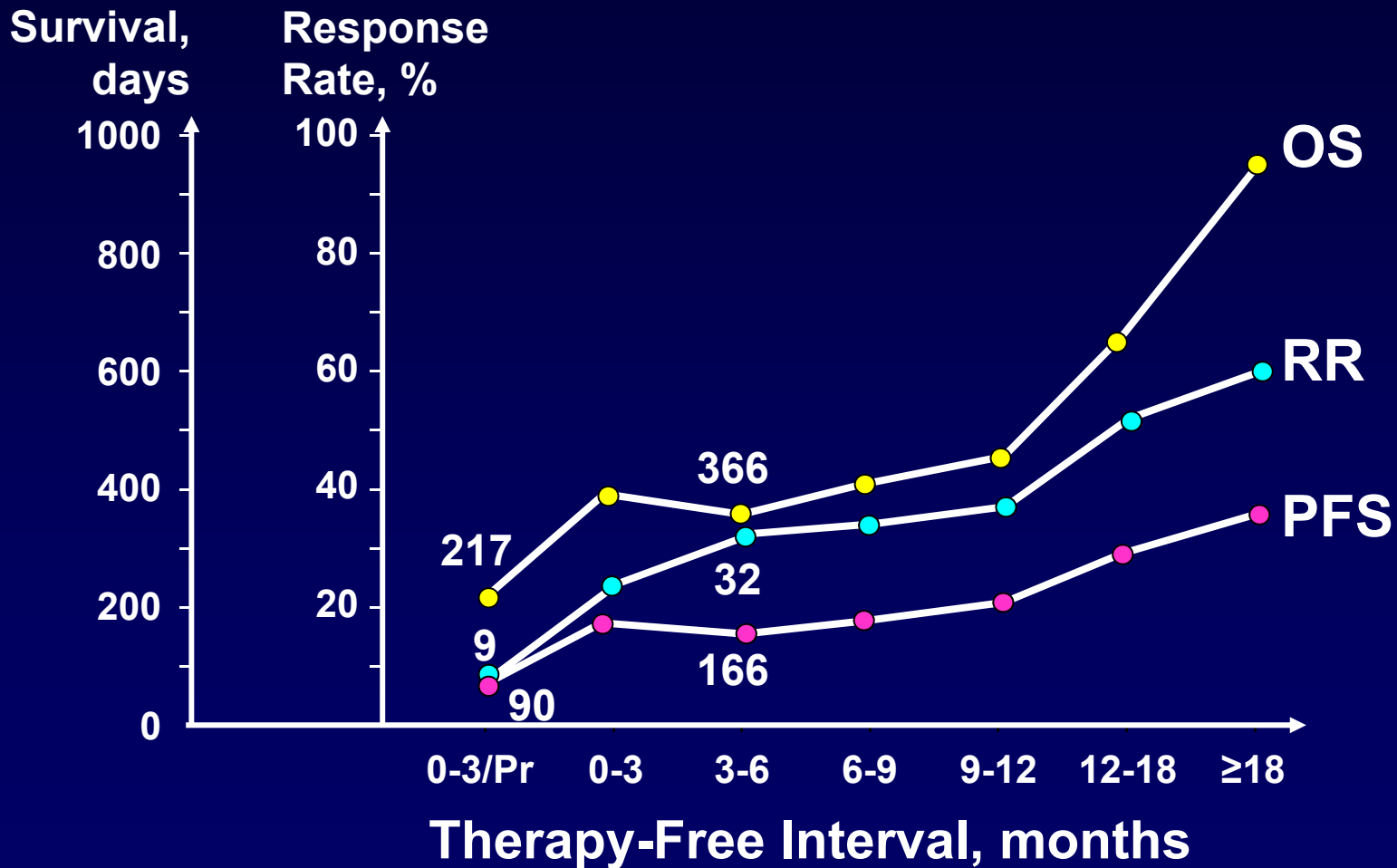
# Background

**RECURRENT  
OVARIAN CANCER  
IS A  
INCURABLE CANCER**

***PLATINUM-  
REFRACTORY / RESISTANT***

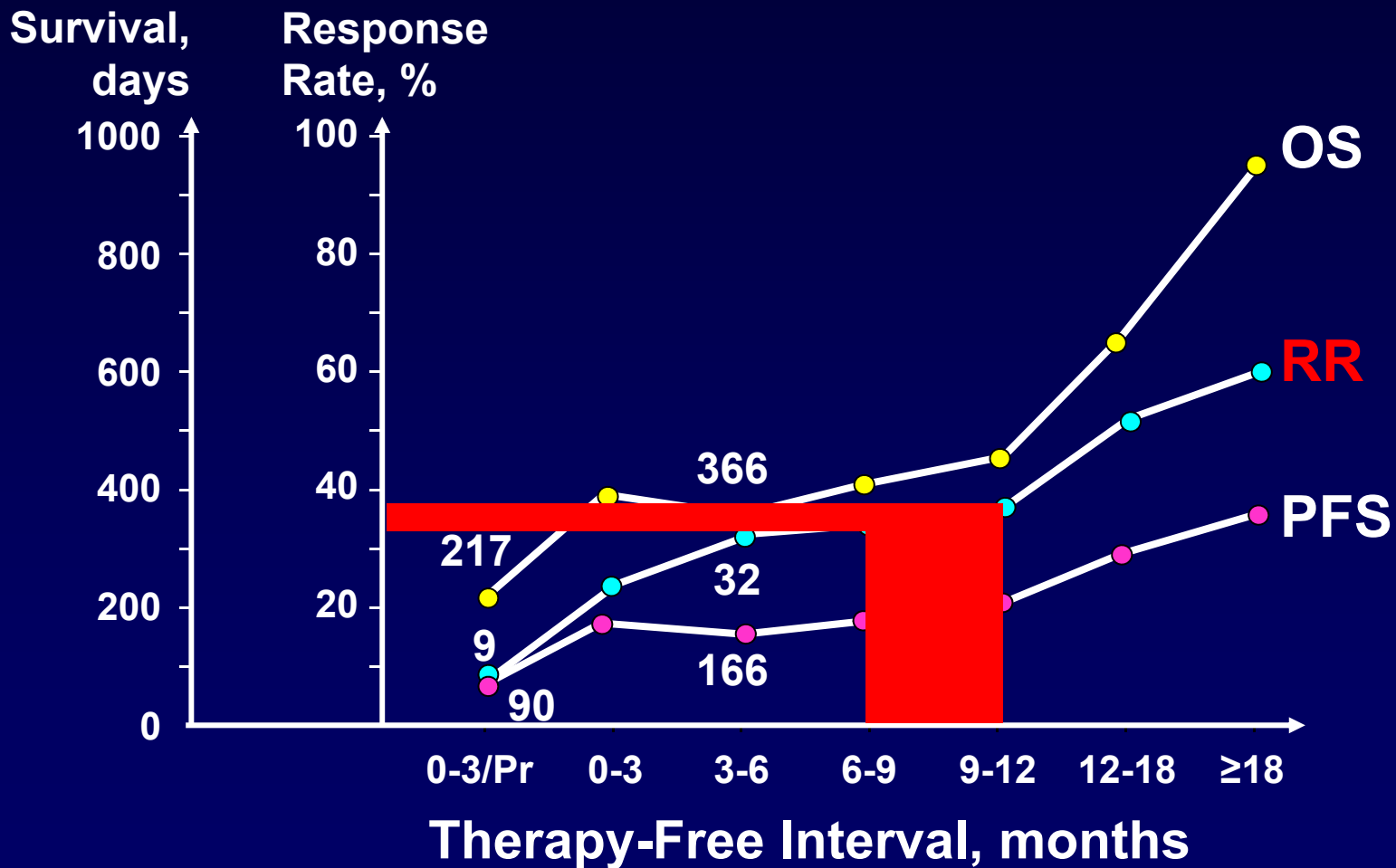
**RECURRENT  
OVARIAN CANCER  
IS A *VERY*  
INCURABLE CANCER**

# Therapy-Free Interval (TFI) and OUTCOME

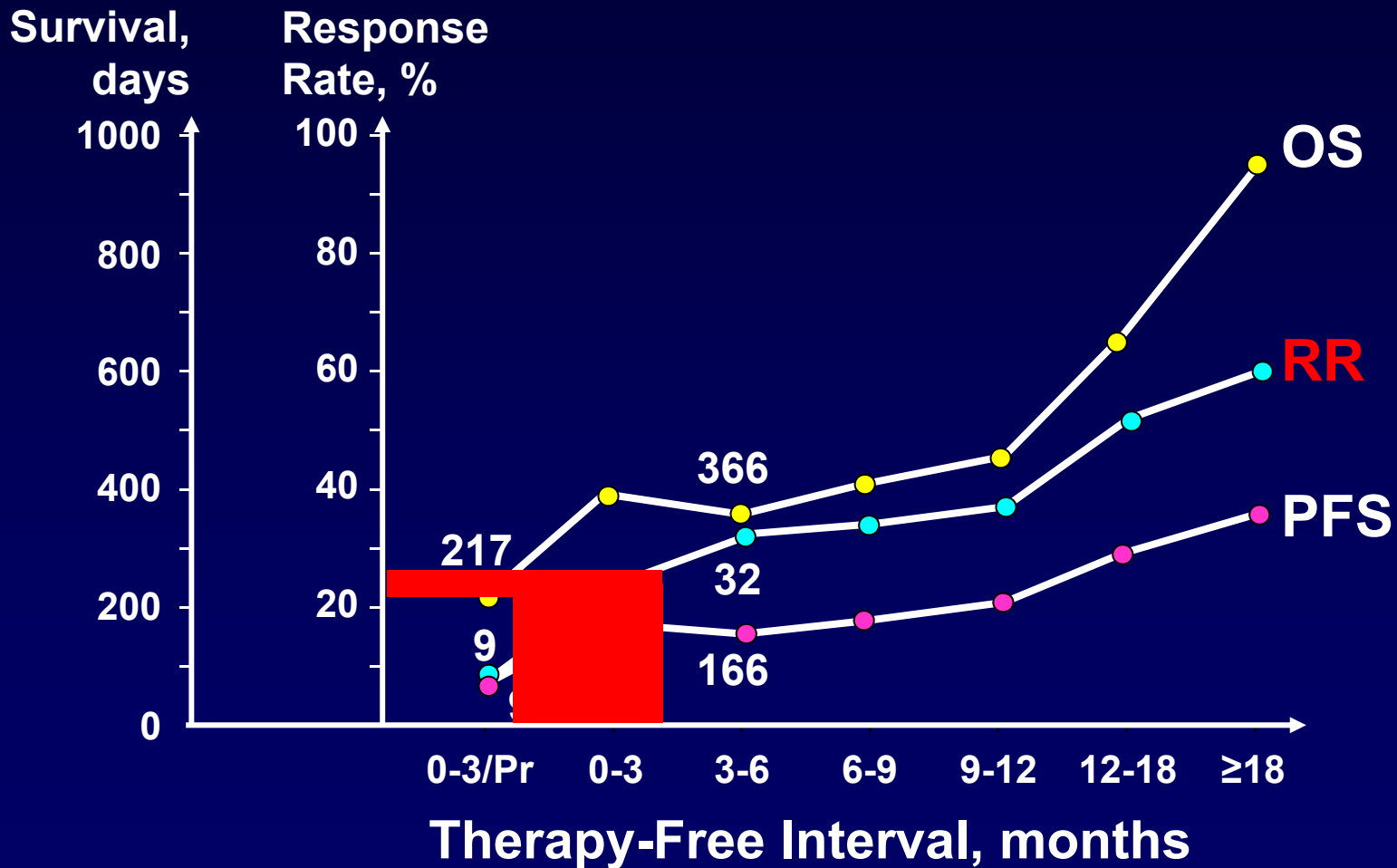


Pujade-Lauraine E, et al. *Proc Am Soc Clin Oncol*. 2002;21: Abstract 829.

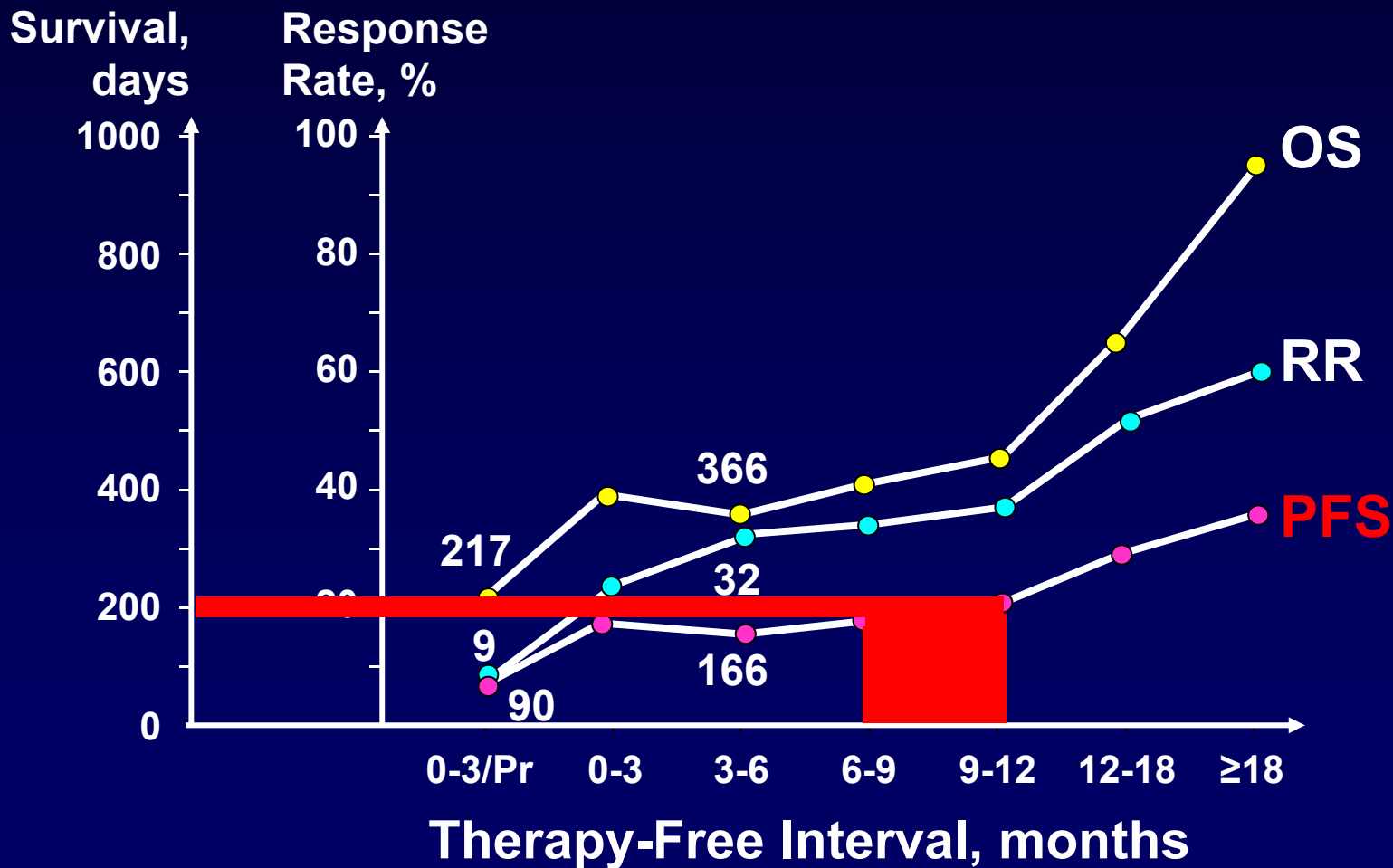
# Therapy-Free Interval (TFI) and OUTCOME Relapse at 6-12 Months



# Therapy-Free Interval (TFI) and OUTCOME Relapse at 0-3 Months

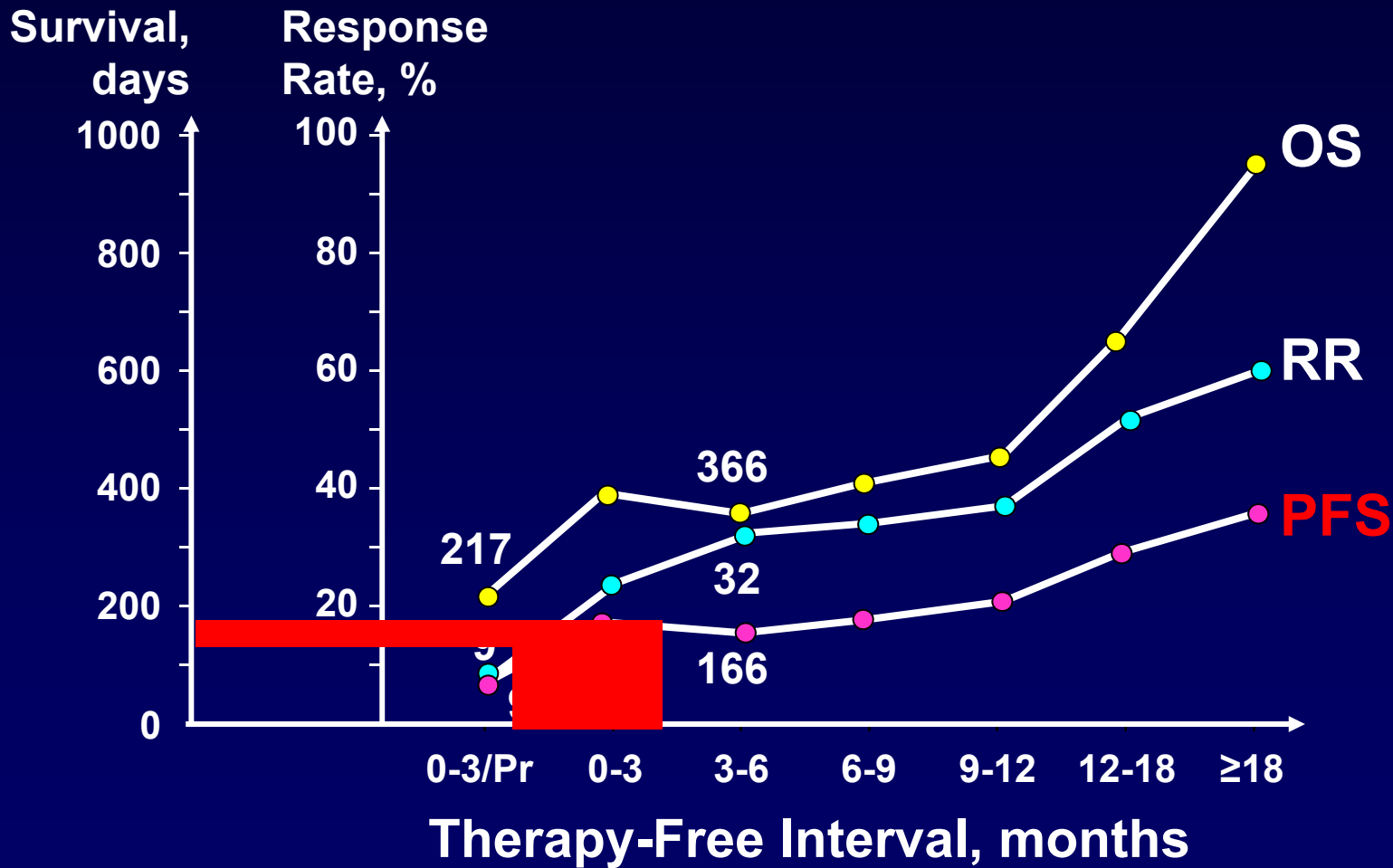


# Therapy-Free Interval (TFI) and OUTCOME Relapse at 6-12 Months



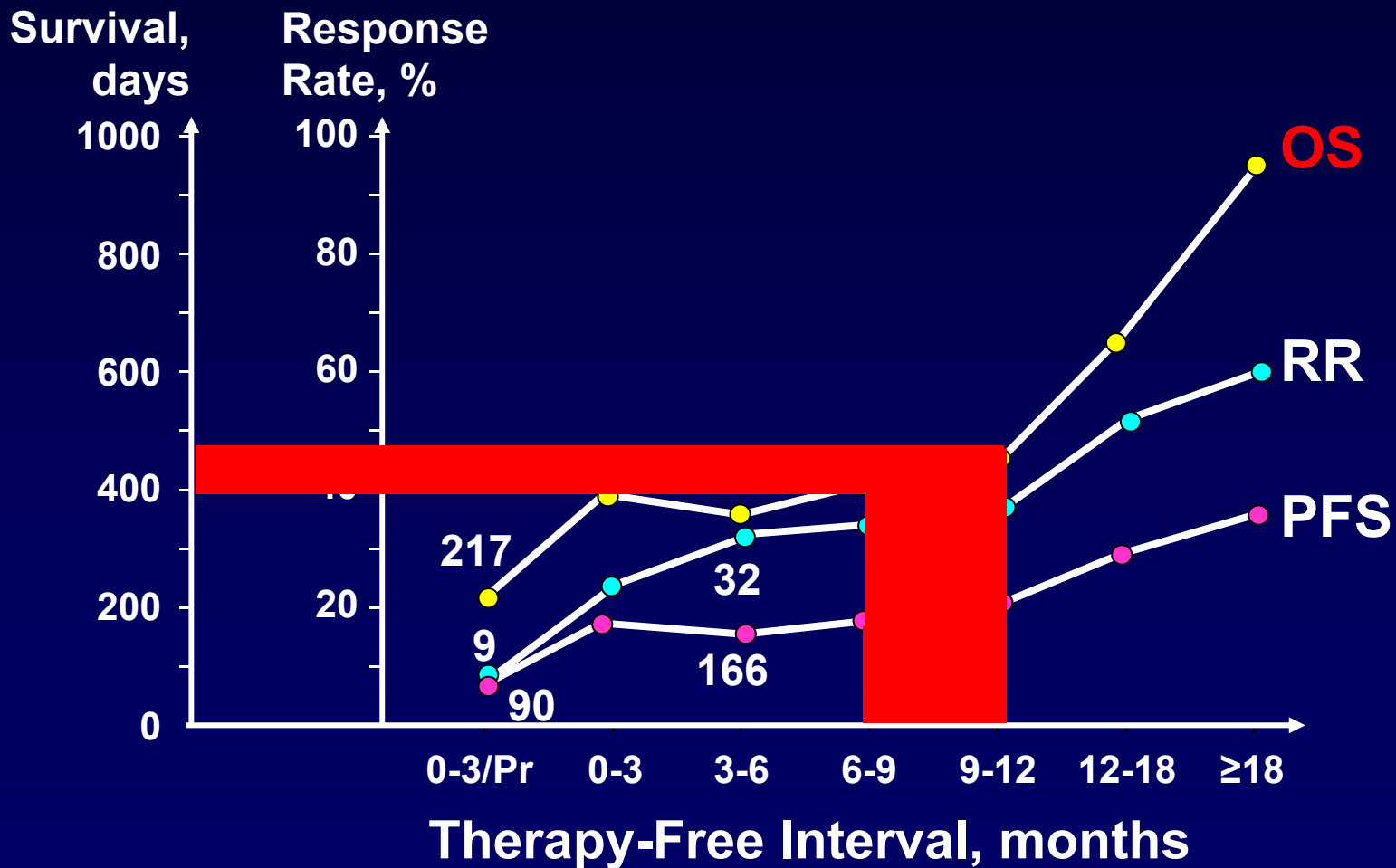
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# Therapy-Free Interval (TFI) and OUTCOME Relapse at 0-3 Months



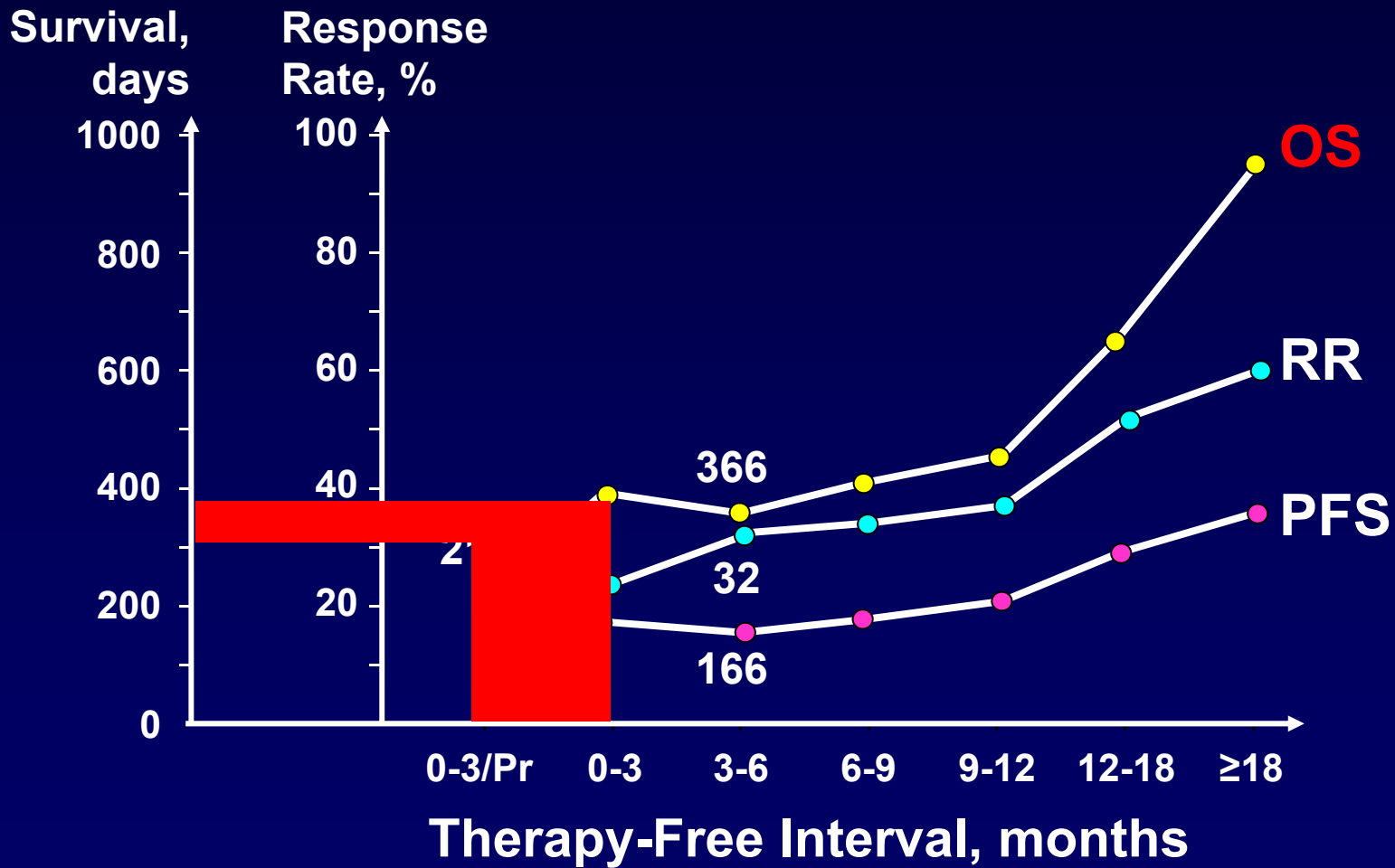
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# Therapy-Free Interval (TFI) and OUTCOME Relapse at 6-12 Months



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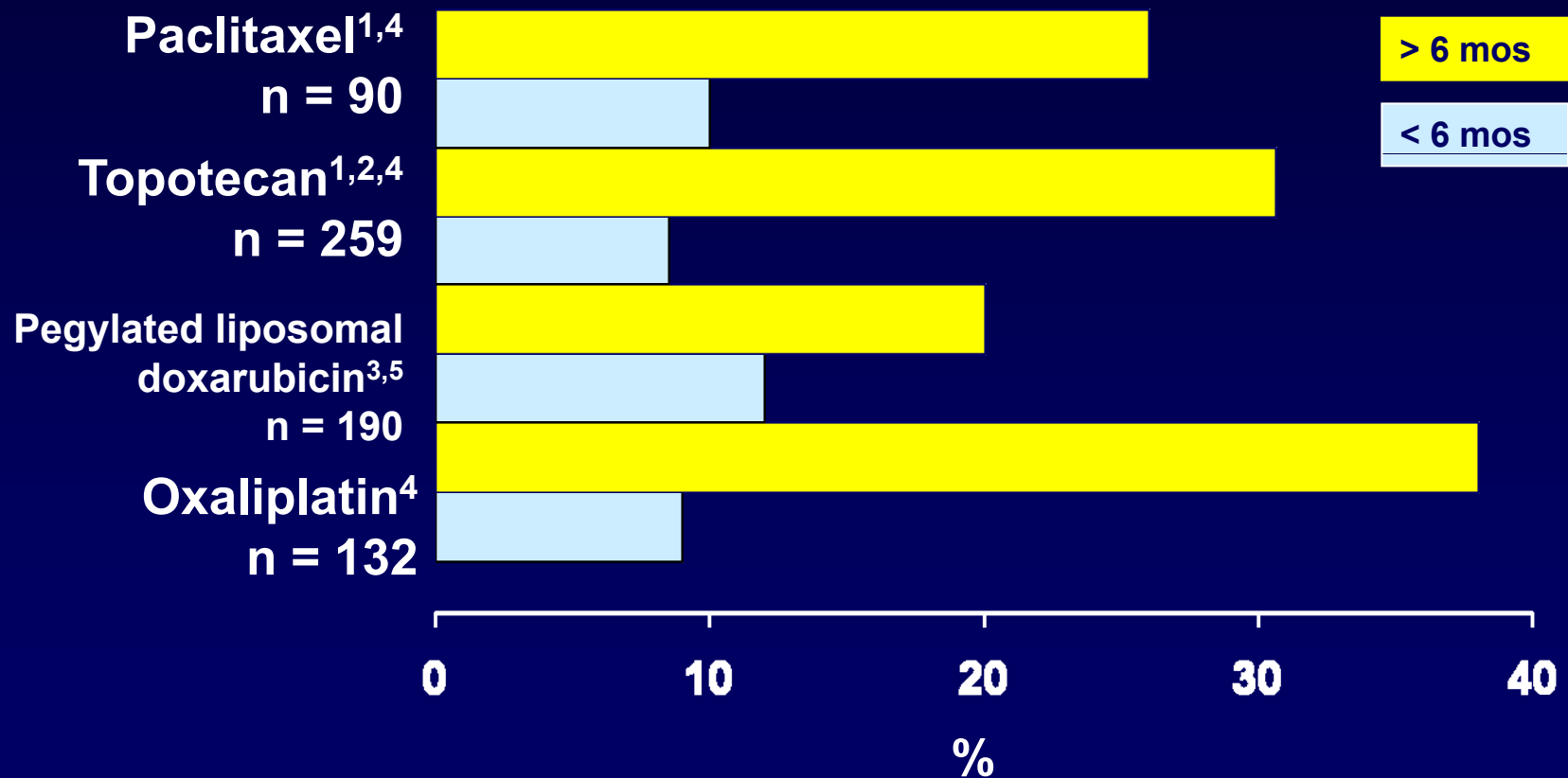
# Therapy-Free Interval (TFI) and OUTCOME Relapse at 0-3 Months



# Single Agents

# RELAPSED OVARIAN CANCER

## Response Rates from RCTs



1. ten Bokkel Huinink W, et al. *J Clin Oncol.* 1997;15(6):2183-2193. 2. Gore M, et al. *Eur J Cancer.* 2002;38(1):57-63.  
3. Gordon AN, et al. *J Clin Oncol.* 2001;19(14):3312-3322. 4. Piccart MJ, et al. *J Clin Oncol.* 2000;18(6):1193-1202.  
5. Mutch D, et al. *Eur J Cancer Suppl.* 2005;3(2): Abstract 910.

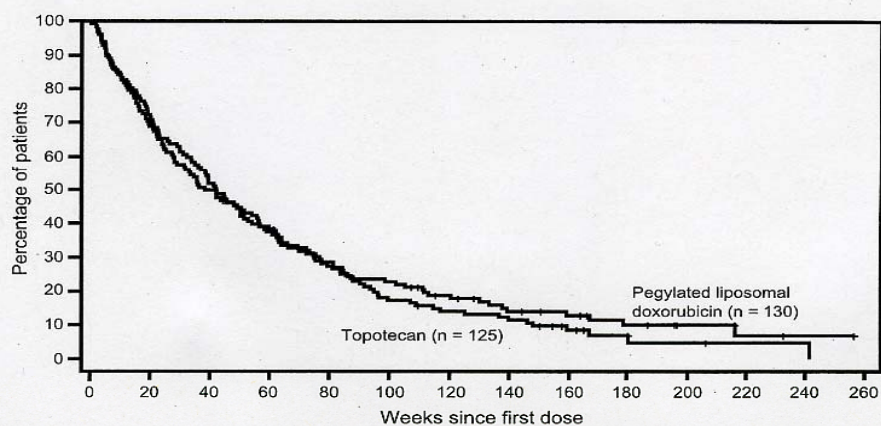
## OVARIAN CANCER

### Relapse < 12 Months, Phase II

Agent	No. of Studies	No. of Patients	Response Rate
Paclitaxel	12	1580	22%
Topotecan	10	882	17%
Pegylated liposomal doxorubicin	4	428	18%
Altretamine	6	235	18%
Etoposide	9	270	20%
Gemcitabine	6	181	18%
Docetaxel	4	166	31%
Epirubicin	6	132	14%
Oxaliplatin	3	118	23%
Vinorelbine	2	71	23%

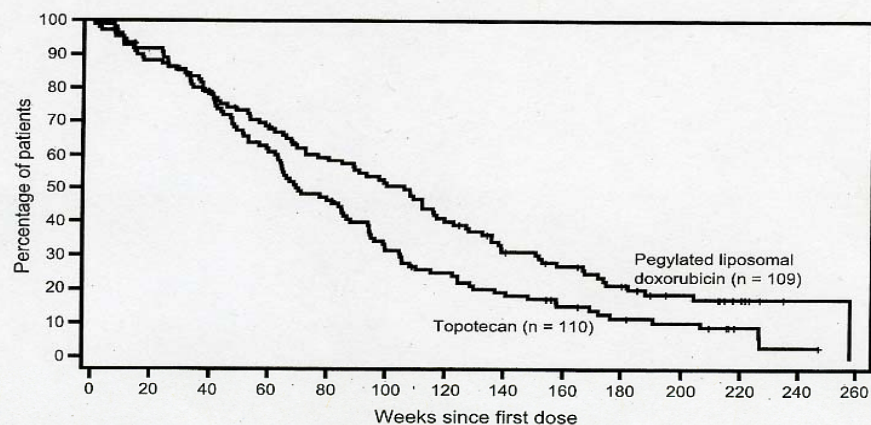
# Pegylated Liposomal Doxorubicin (PLD) vs TOPOTECAN

## Platinum-refractory disease



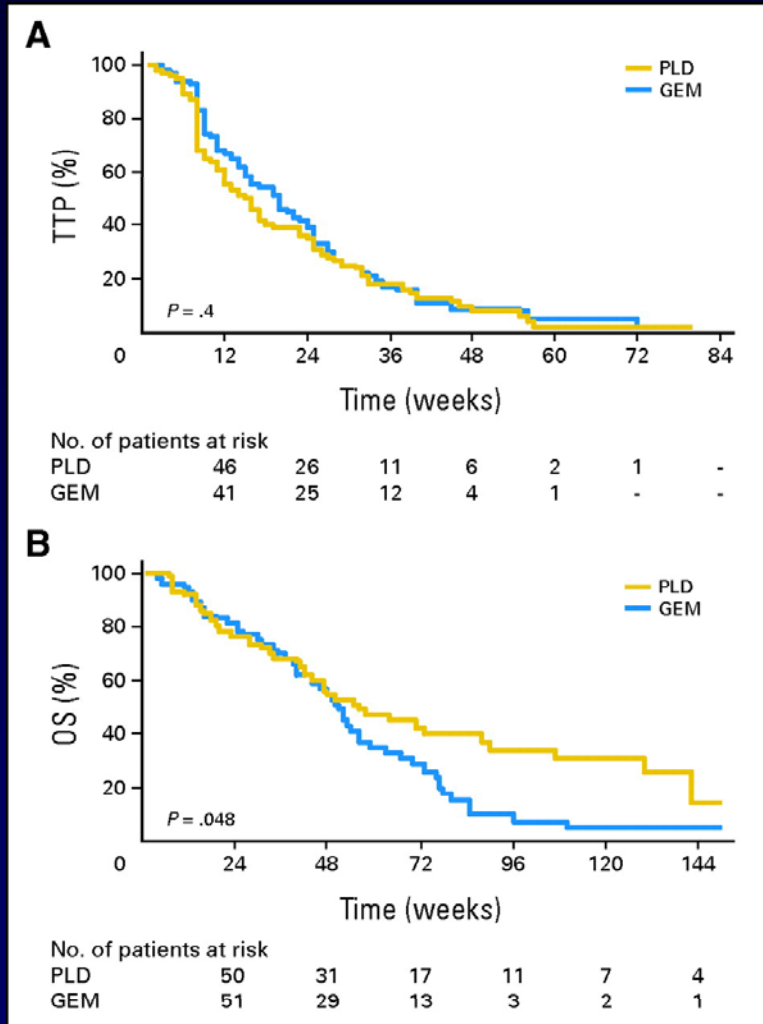
**n = 255 (<6 mos)**  
**HR = 1.07 (95% CI: 0.82-1.39)**  
**P = .68**

## Platinum-sensitive disease



**n = 219 (>6 mos)**  
**HR = 1.43 (95% CI: 1.07-1.9)**  
**P = .017**

# Gemcitabine vs PLD Recurrence <12 Months



153 pts randomised  
 OR 29% Gem vs 16% PLD  
 $P = .066$

TTP 14 weeks no difference

OS PLD vs Gem ITT  
 (56 weeks vs 51 weeks,  $P = .048$ )  
OS patients 7-12 months  
 benefit for PLD ( $P = .013$ )

# TOPOTECAN vs TREOSULPHAN

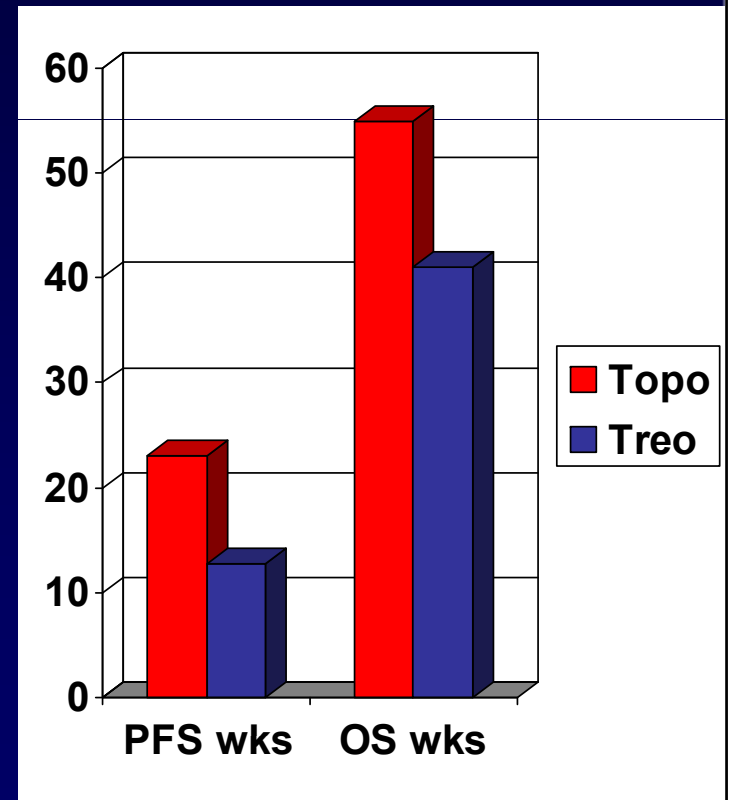
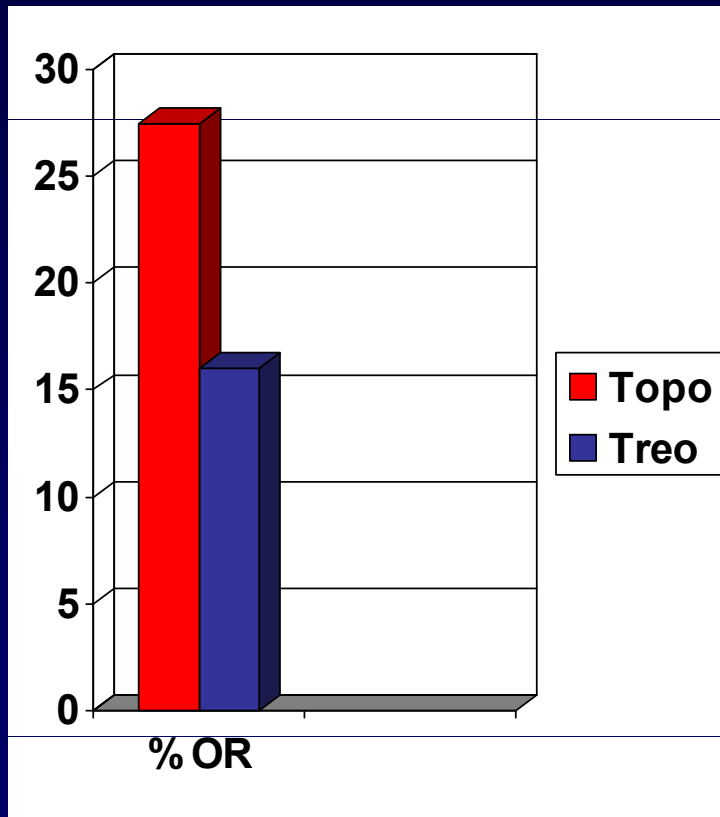
## Relapse 0-12 Months

Topotecan

1.5 mg/m<sup>2</sup> iv daily x5, q21

Treosulphan 7 g/m<sup>2</sup> iv q21

- 274 patients
- OR  $P = .03$
- PFS  $P = .002$
- OS  $P = .002$



# **A Phase II Study of Patupilone in Platinum-Refractory/Resistant Ovarian Cancer**

**112 patients evaluable  
Patupilone 10 mg/m<sup>2</sup> iv q21**

**PR 7.1%**

**SD 41%**

**PFS, median 2.5 mos**

**OS, median 11.2 mos**

# Topotecan Weekly Versus 5-day P-Resistant Ovarian Cancer (TOWER)

**154 patients evaluable**

**Weekly Topotecan 4 mg/m<sup>2</sup> D 1,8,15 q28**

**vs**

**Standard Topotecan 1.25 mg/m<sup>2</sup> D1-5 q21**

**SD/PR/CR 47% vs 57%**

**Median PFS 3.2 months vs 4.4 months**

**Median OS 9.8 months vs 10.0 months**

# **RELAPSED OVARIAN CANCER**

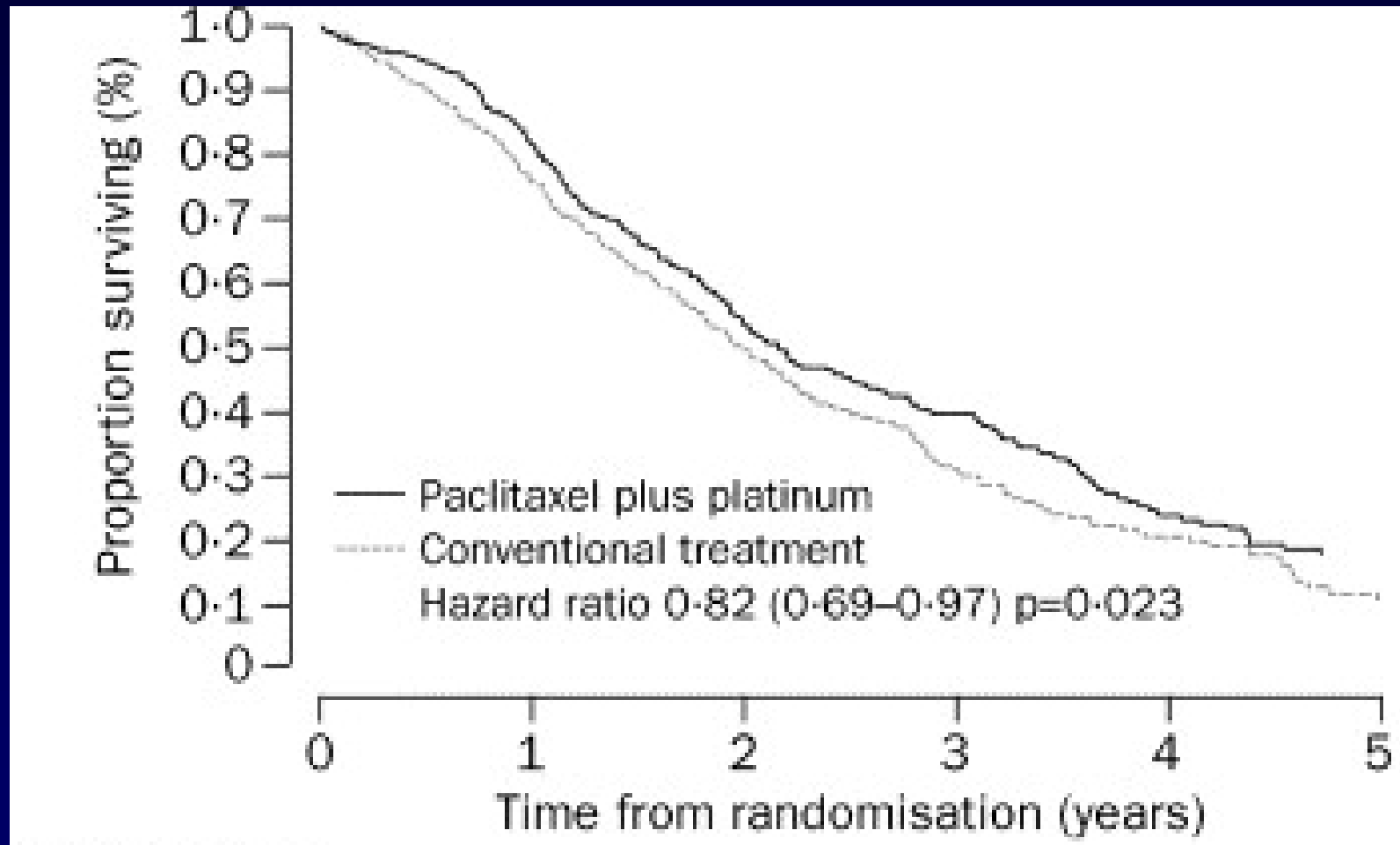
## **Weekly Therapy**

**Low peak plasma concentration**  
→ **low toxicity**

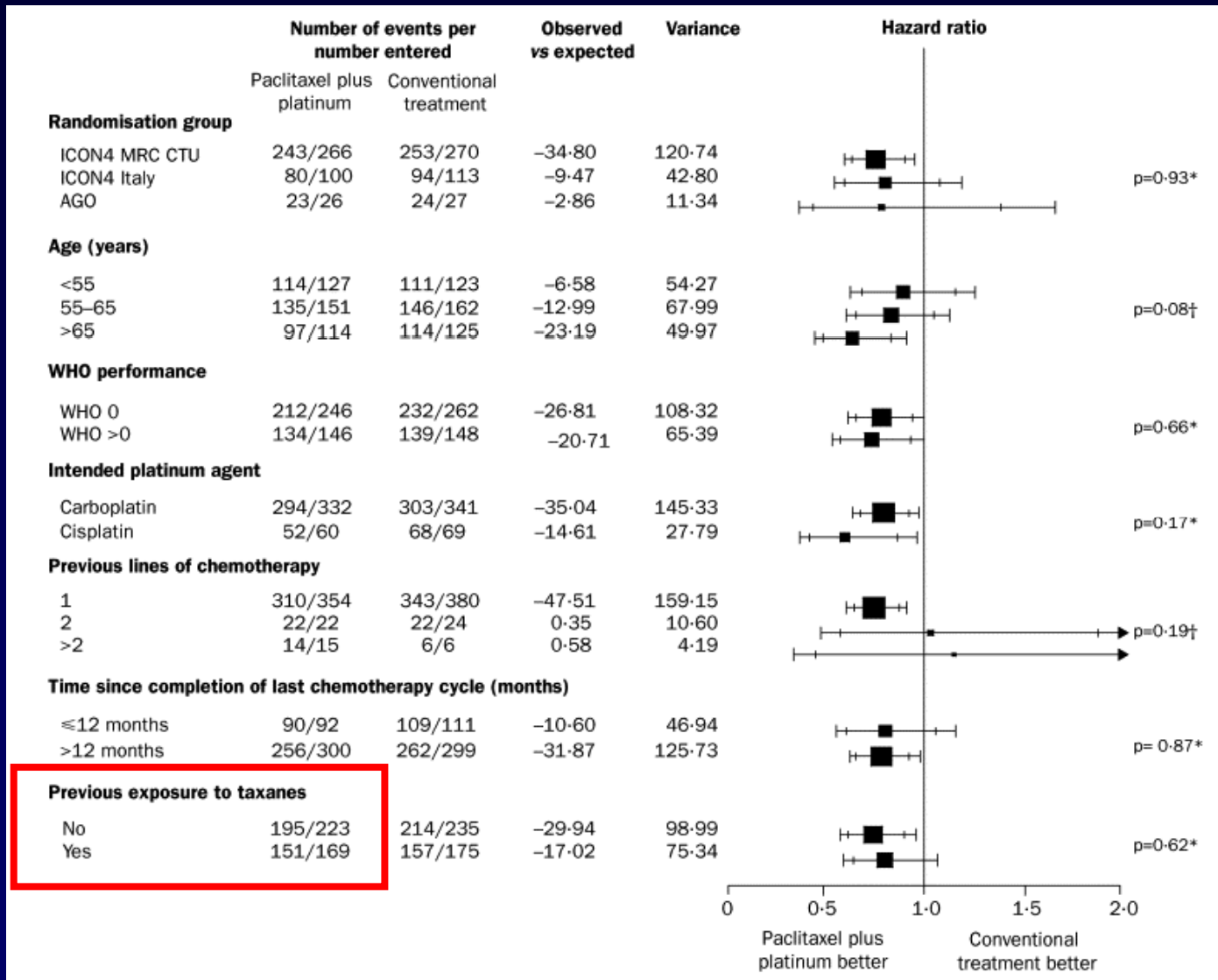
**Increase dose density**  
→ **increase efficacy**

# Combination Therapy

# ICON 4 Overall Survival



# ICON 4 Subset Analyses

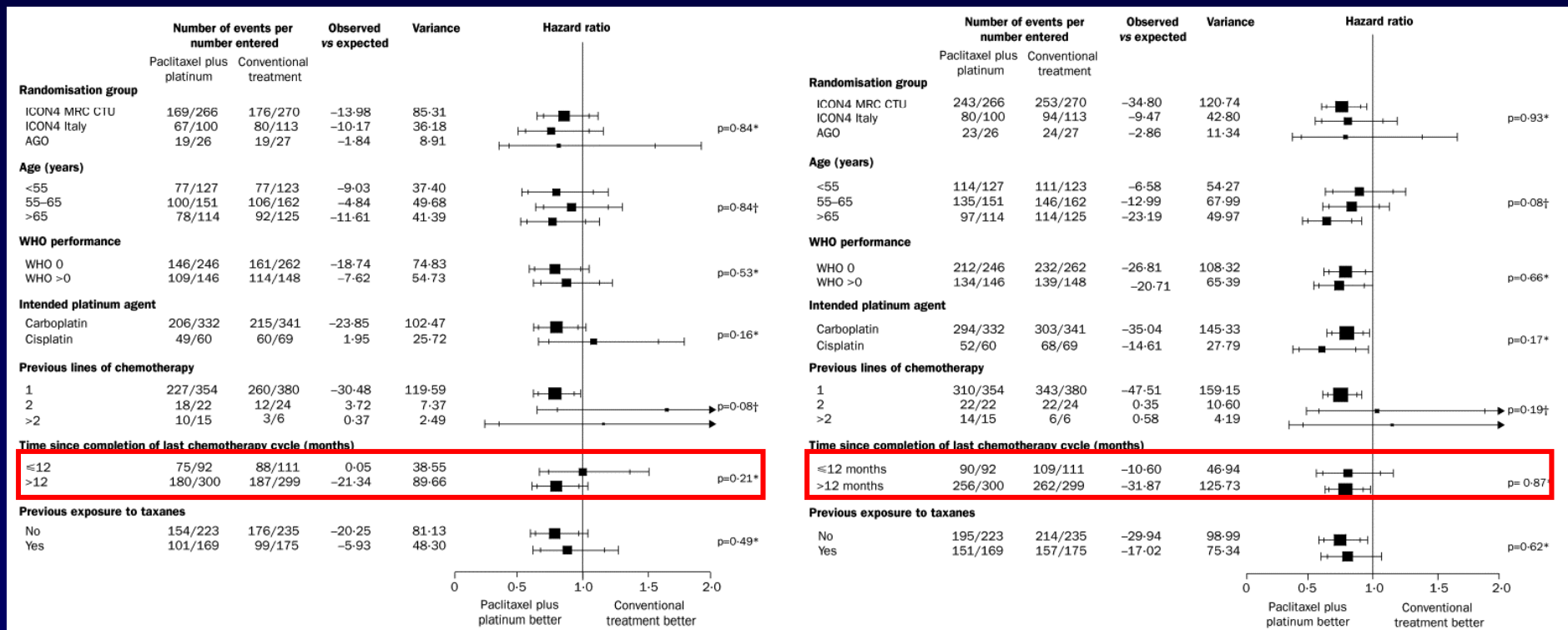


Parmar MK, et al. *Lancet*. 2003;361(9375):2099-106.

# ICON 4 Subset Analyses

## Overall survival

## Progression-free survival



# RELAPSED OVARIAN CANCER

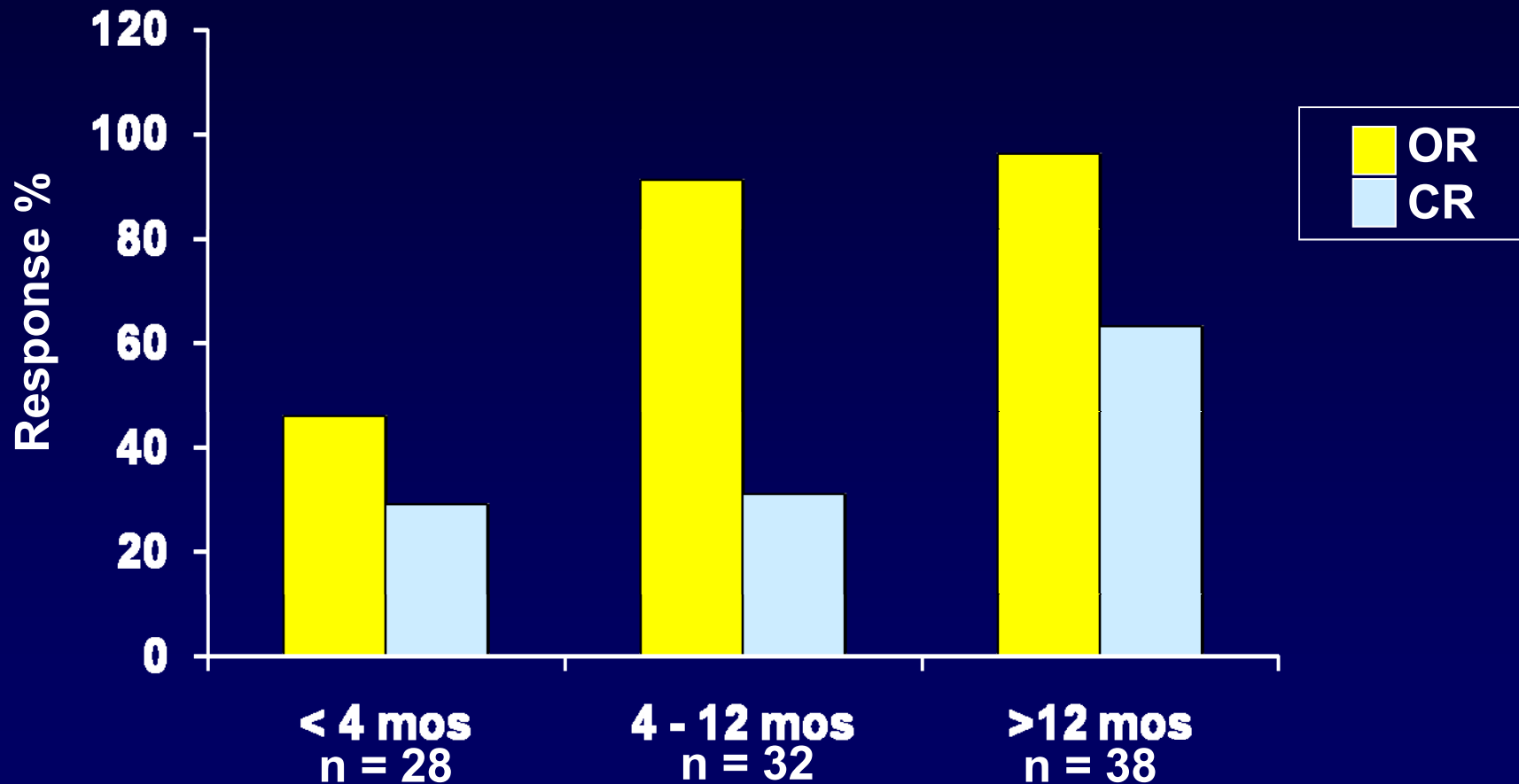
**Cisplatin 50 – 70 mg/m<sup>2</sup>  
weekly, x 6**

**+**

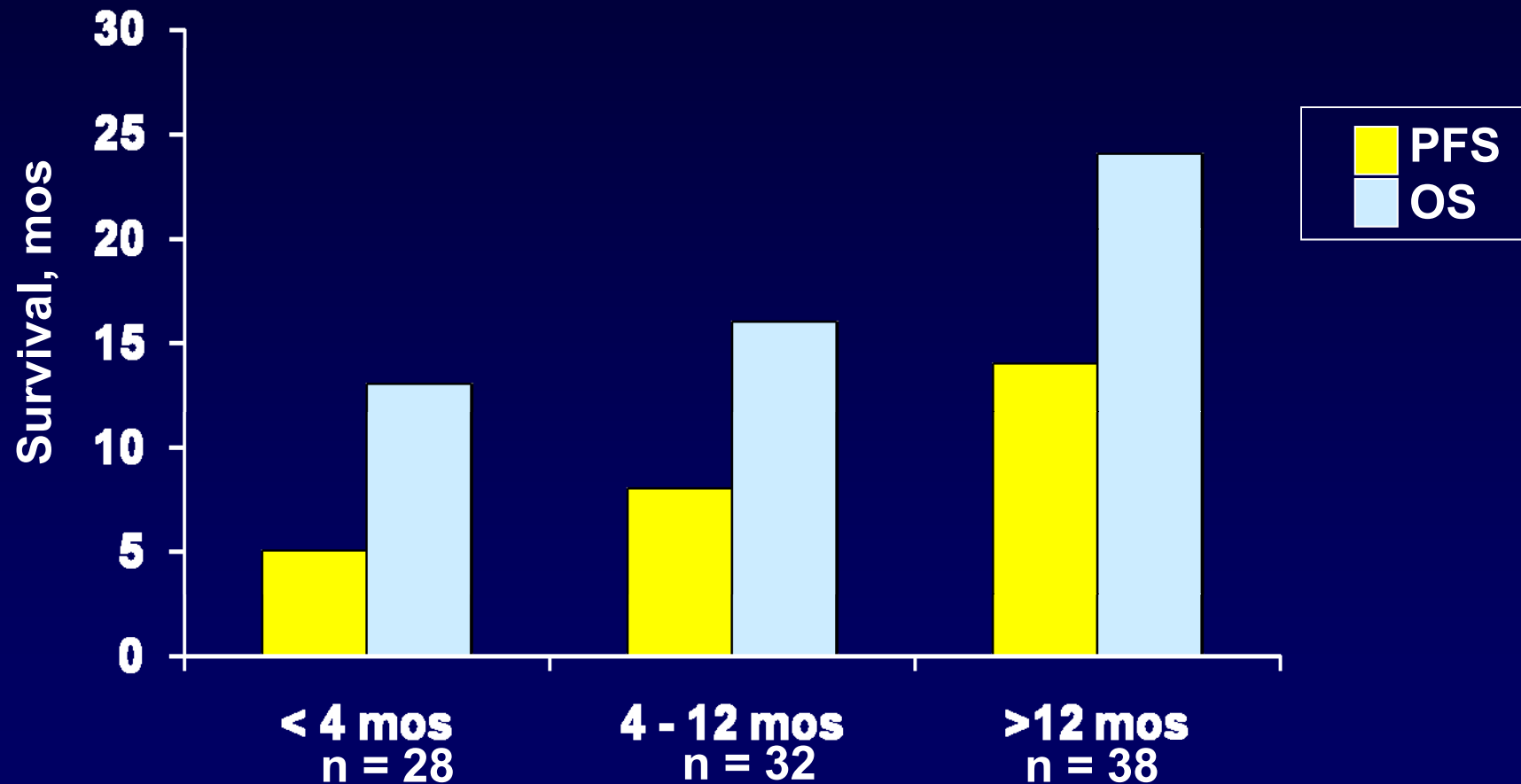
**Etoposide 50 mg PO od**

**Toxic / nontoxic  
? hypertonic saline**

# Response Rate in RELAPSED Ovarian Cancer



# PFS and OS in RELAPSED Ovarian Cancer



# **Extended Weekly Dose-Dense Carbo-Paclitaxel P-Resistant/Recurrent Ovarian Cancer <12 Months**

**20 patients**

**Carboplatin AUC 3 + Pac 70 mg/m<sup>2</sup>**

**Day 1, 8, 15 q 4-wkly x6**

**OR (RECIST) 60%**

**OR (CA125) 76%**

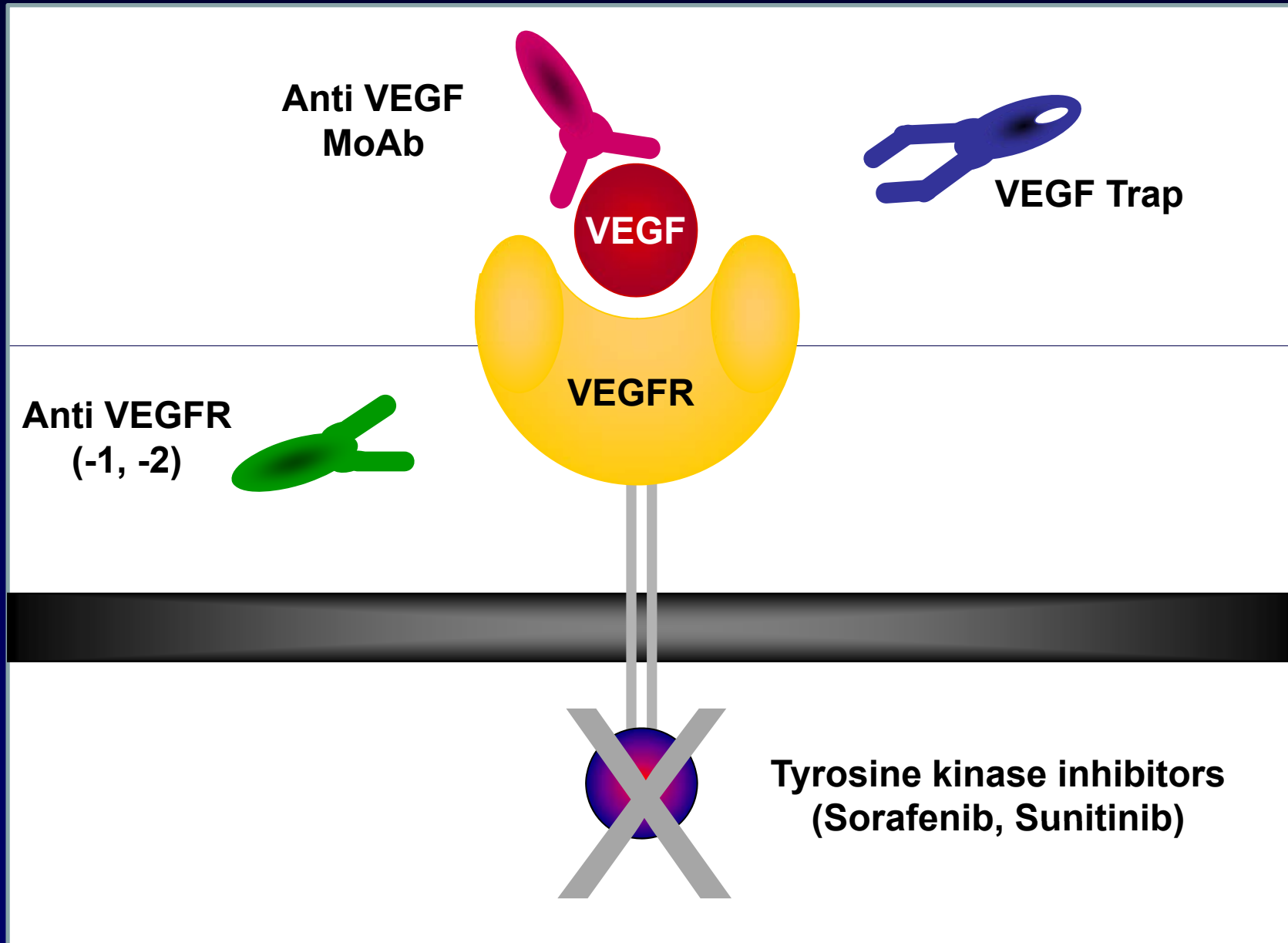
**PFS median 7.9 months**

**OS median 13.3 months**

# Newer Agents



# TARGETING VEGF PATHWAY

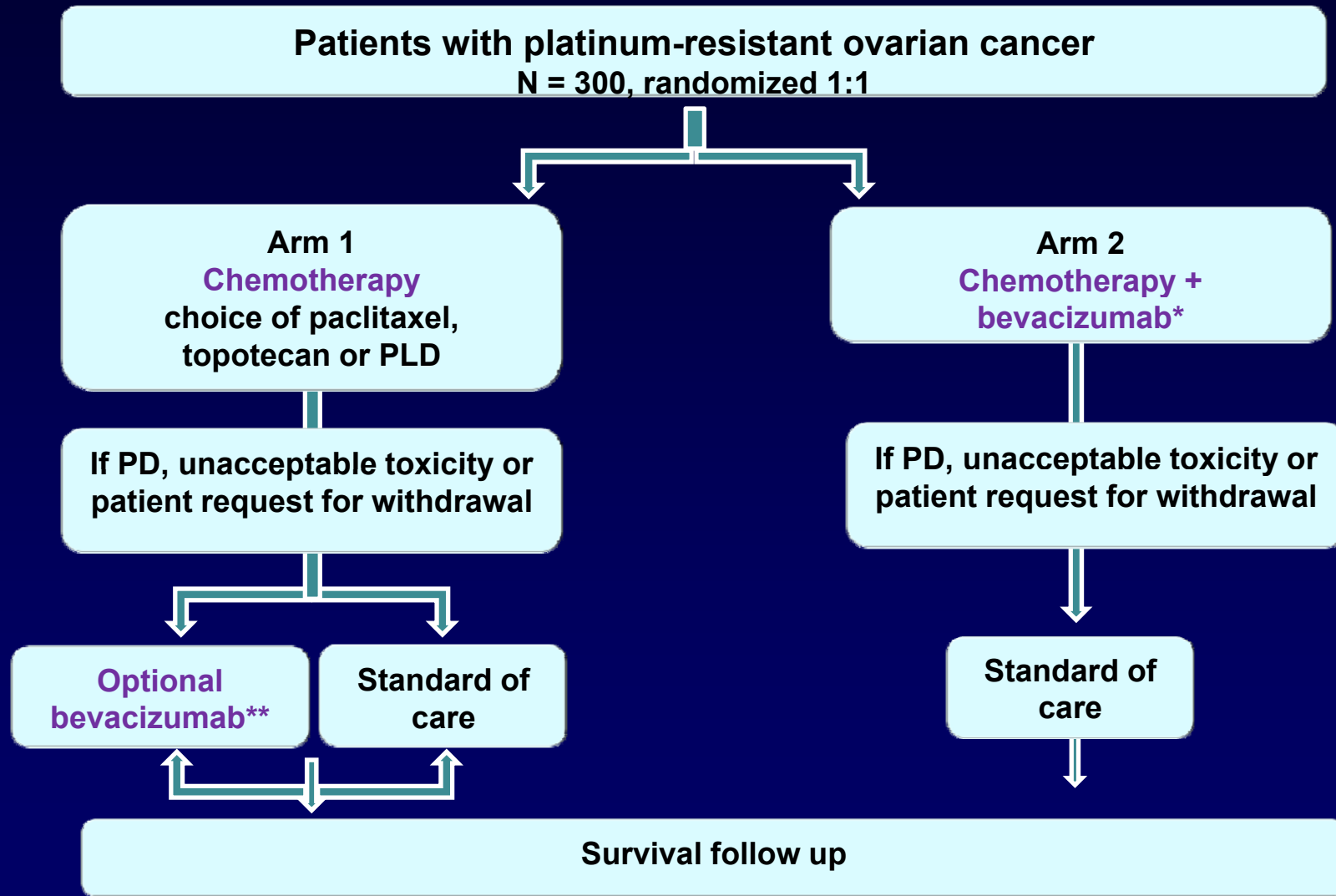


# OVARIAN CANCER

## Bevacizumab Phase II Studies

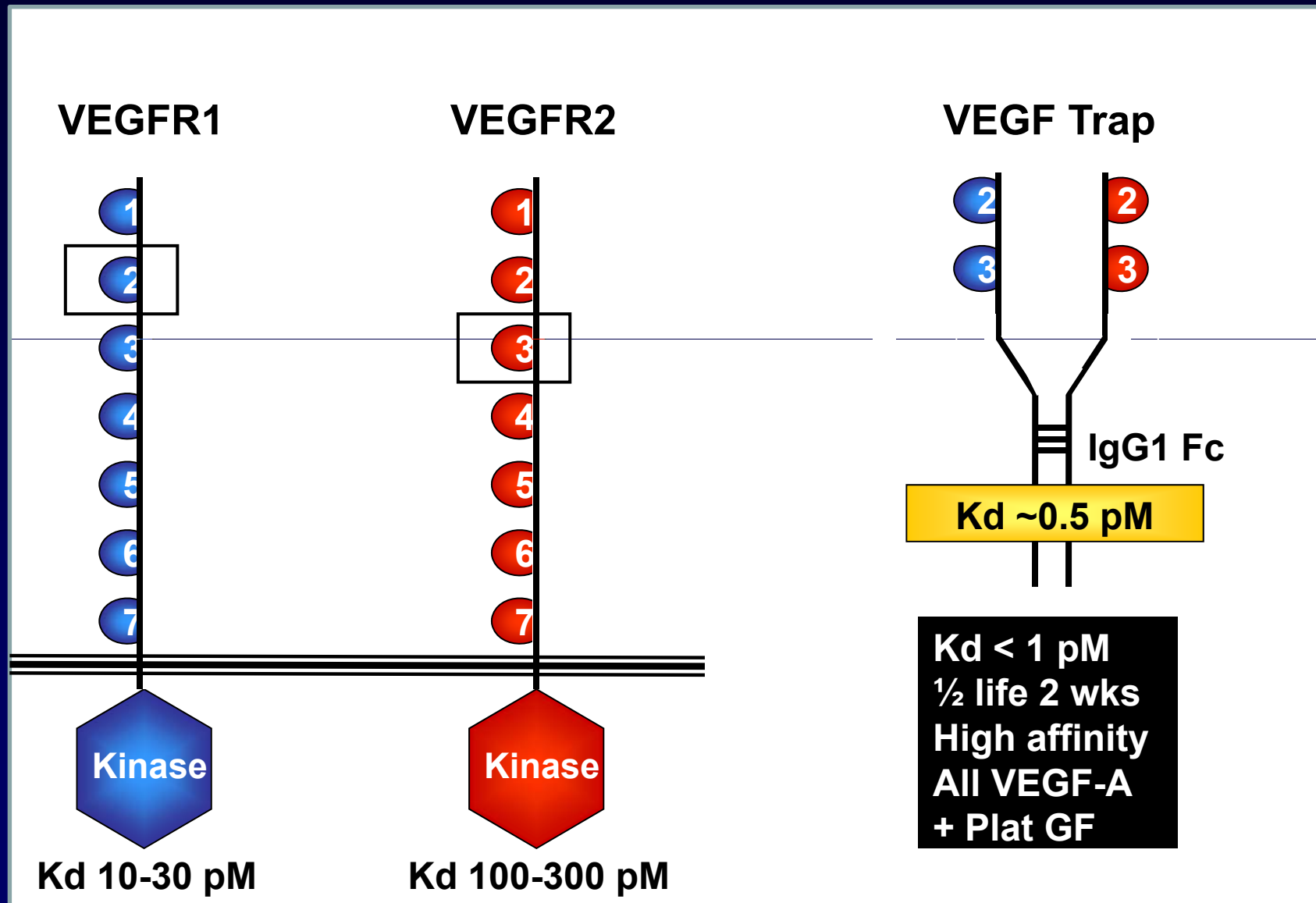
Study	n	Bev Dose	Response Rate	Duration of Response	Disease-Free at 6 Months
<b><u>PHASE 2</u></b>					
Burger 2005	62	15 mg/kg q21	18%	10.3 mos	39%
Garcia 2005	29	10 mg/kg biweekly	28%	5 mos	57%
Cannistra 2006	44	15 mg/kg q21	16%	12 wks	27%
Penson 2006	30	15 mg/kg q21	NR	NR	NR
Friberg 2006	13	15 mg/kg q21	8%	NR	NR
<b><u>RETROSPECTIVE</u></b>					
Wright 2006	62	NR	36%	NR	NR
Monk 2006	32	15 mg/kg q21	16%	NR	PFS 5.5 mos
Wright 2006	23	5 mg/kg/wk alt weeks	35%	5.6 mos	13%
Bidus 2006	3	15 mg/kg q21	100%	15–22 mos	NR
Cohn 2006	10	10 mg/kg biweekly	NR	NR	NR

# AURELIA: Avastin Use in REsistant ovarian epitheLIAI cancer



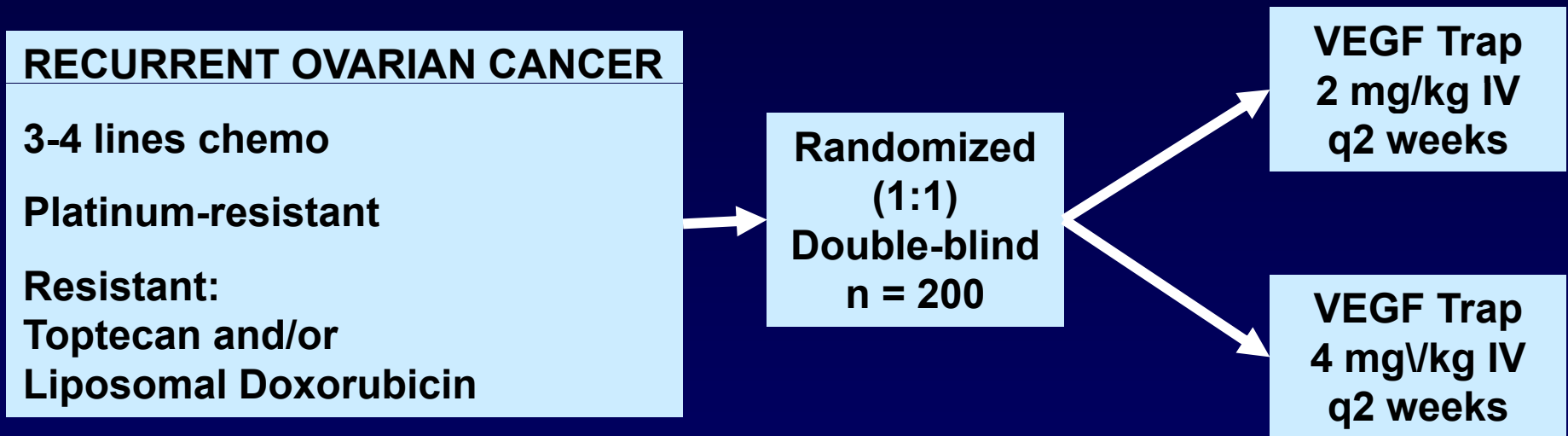
\*10 mg/kg IV q2w (15 mg/kg q3w will be used instead if topotecan is selected and administered at a dose of 1.25 mg/m<sup>2</sup> on a 1–5/q3w schedule); \*\* 15 mg/kg i.v. q3w; PLD, Pegylated liposomal doxorubicin; PD, progressive disease

# STRUCTURE OF VEGF TRAP



# PHASE II TRIAL VEGF TRAP

## Ovarian Cancer

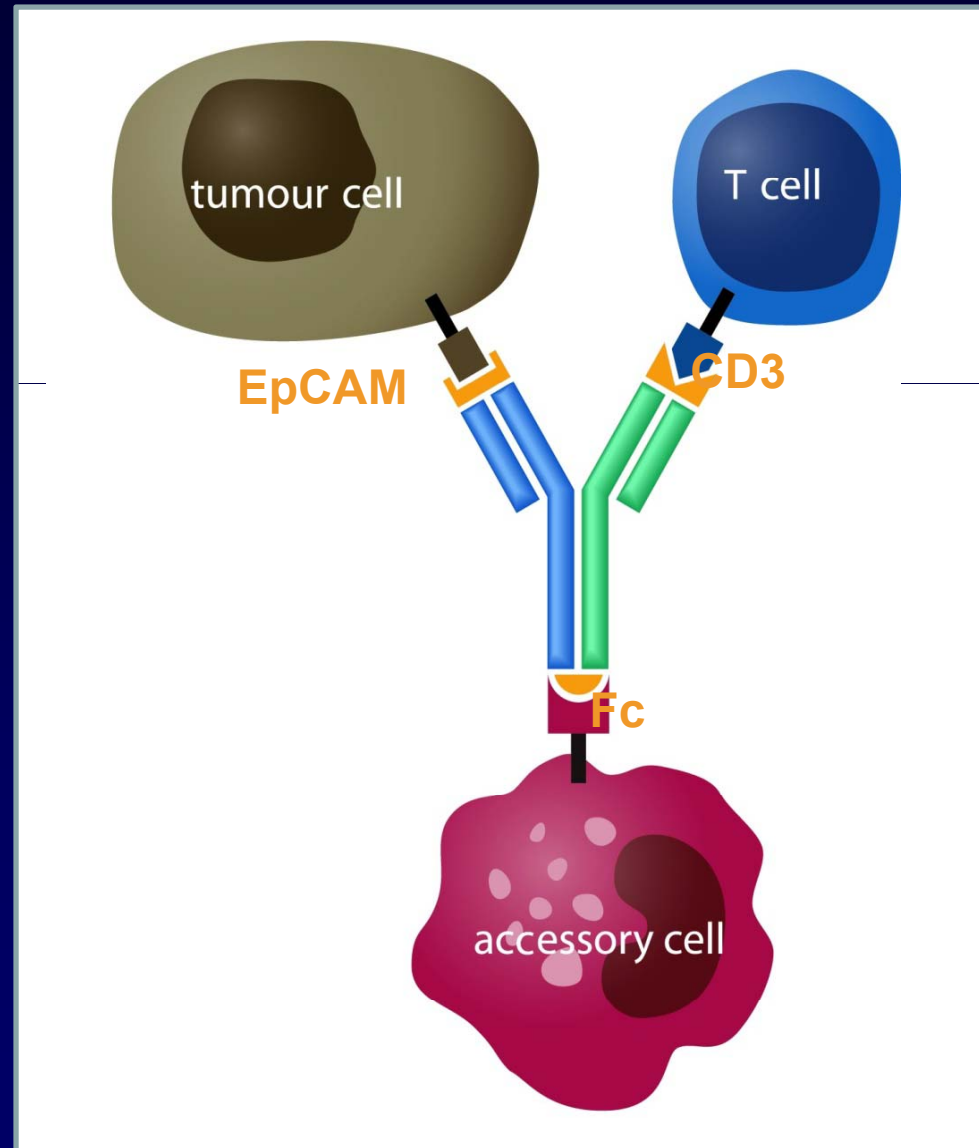


# **VEGF Trap**

## **Blinded Pooled Data, 162 patients**

<b>CR / PR</b>	<b>8%</b>
<b>CA 125 PR</b>	<b>13%</b>
<b>SD &gt;3 mos</b>	<b>41%</b>
<b>Ascites CR</b>	<b>29% (n = 23)</b>

# Catumaxomab



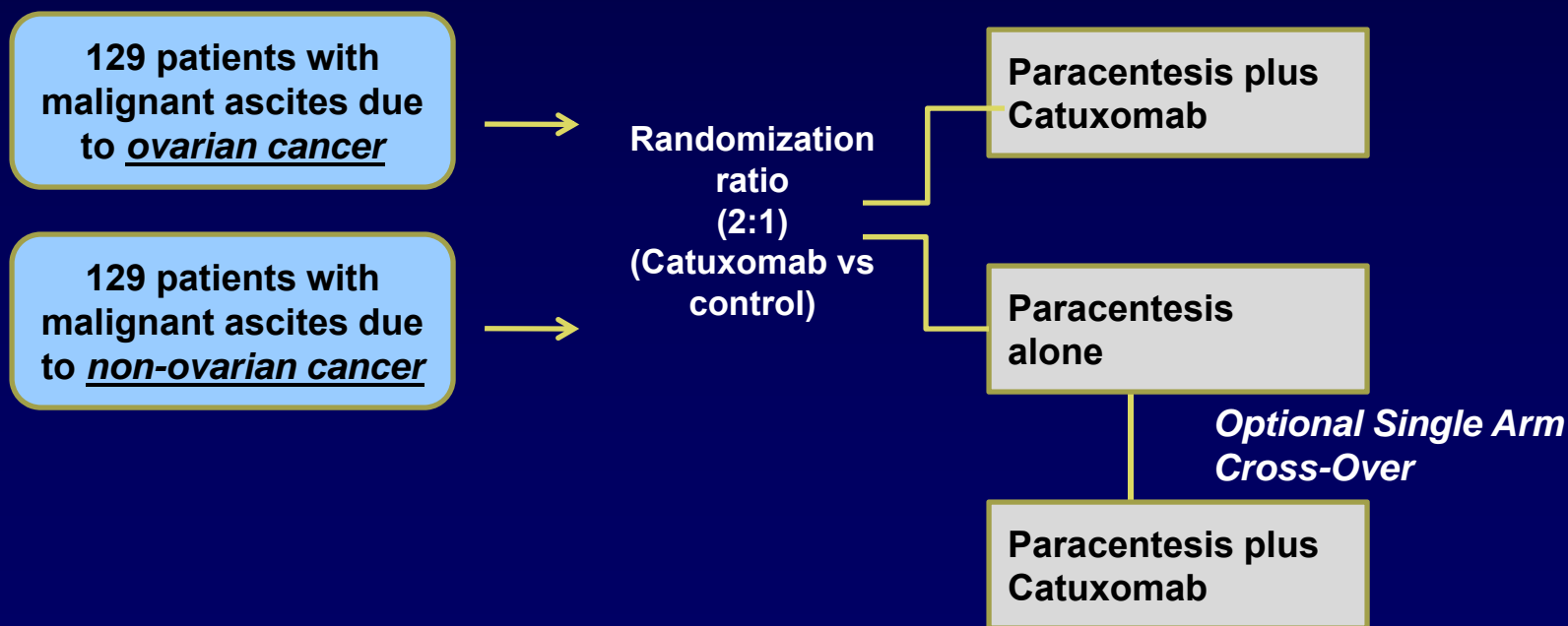
# Catumaxomab

## Trifunctional Antibody Targeting EpCAM

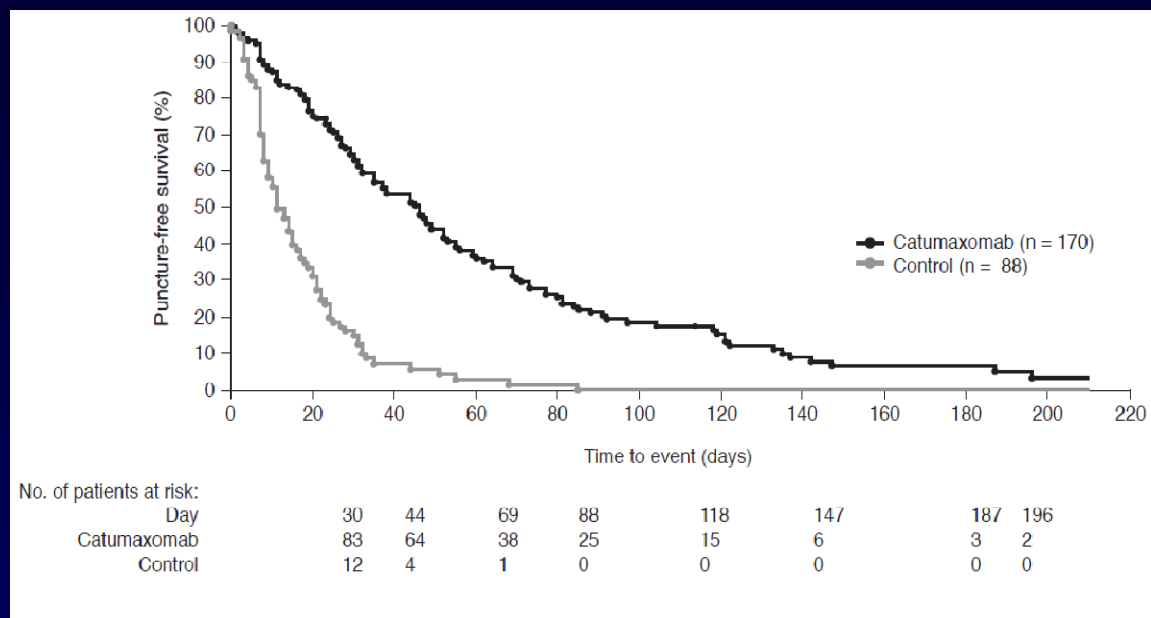
- **Epithelial Cell Adhesion Molecule (EpCAM) is an appropriate target for intraperitoneal therapy**
  - **The vast majority of epithelial tumors express EpCAM**
  - **> 90% of ovarian cancer and gastric tumors express EpCAM**
  - **Cells of the peritoneum do not express EpCAM →tumor-specific targeting**

# 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 ip infusions at 10, 20, 50, and 150  $\mu\text{g}$  of catumaxomab on day 0, 3, 7, and 10



# Puncture-Free Survival (Primary Endpoint)



	Pooled Population	Ovarian Cancer Stratum
Catumaxomab (Number of patients with event)	46 (119)	52 (56)
Control (Number of patients with event)	11 (82)	11 (42)
Difference [Factor]	35 [4.2]	41 [4.7]
<i>P</i> value (log-rank test)	<.0001	<.0001

# RELAPSE AT 6-12 MOS

**BAD  
PROGNOSTIC  
GROUP**

**SAME CHEMO  
SHORTER  
REMISSION**

**SAME CHEMO  
SAME TOXICITY**

**COMBINATION  
P-BASED Rx  
TOXIC**

# RELAPSE AT 6-12 MOS

BAD  
PROGNOSTIC  
GROUP

SAME CHEMO  
SHORTER  
REMISSION

SAME CHEMO  
SAME TOXICITY

COMBINATION  
P-BASED Rx  
TOXIC

SEPARATE  
TRIAL  
GROUP

# Treatment Algorithm

Stage III/IV Ovarian Cancer



First-Line therapy  
Carboplatin/paclitaxel

Platinum-sensitive  
(relapse >12 mo)  
Platinum partially sensitive  
(relapse 6-12 mo)

Re-challenge with platinum:  
Carboplatin-PLD,  
carbo- paclitaxel,  
carbo-gemcitabine  
Trabectedin/PLD

Platinum-resistant /  
refractory  
(relapse <6 mo  
or no response)

PLD  
Topotecan  
Weekly Carbo/paclitaxel  
Experimental drugs