How to approach patients in relapse

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Disclosure

- **Advisory board, teaching lectures honoraria: Roche, Merck, Pharmamar, Sanofi, Lilly, Boehringer-Ingelheim, GSK, Esai**

When a patient is considered to be in relapse?

- In the follow-up of a patient, CA-125 level rose from 16 U/ml up to 62 U/ml (Nl<30 U/ml)
- and continued to rise over the next 2 months to 96 U/ml
- she is asymptomatic and CT-scan remained normal

GCIG definition of relapse according to CA125

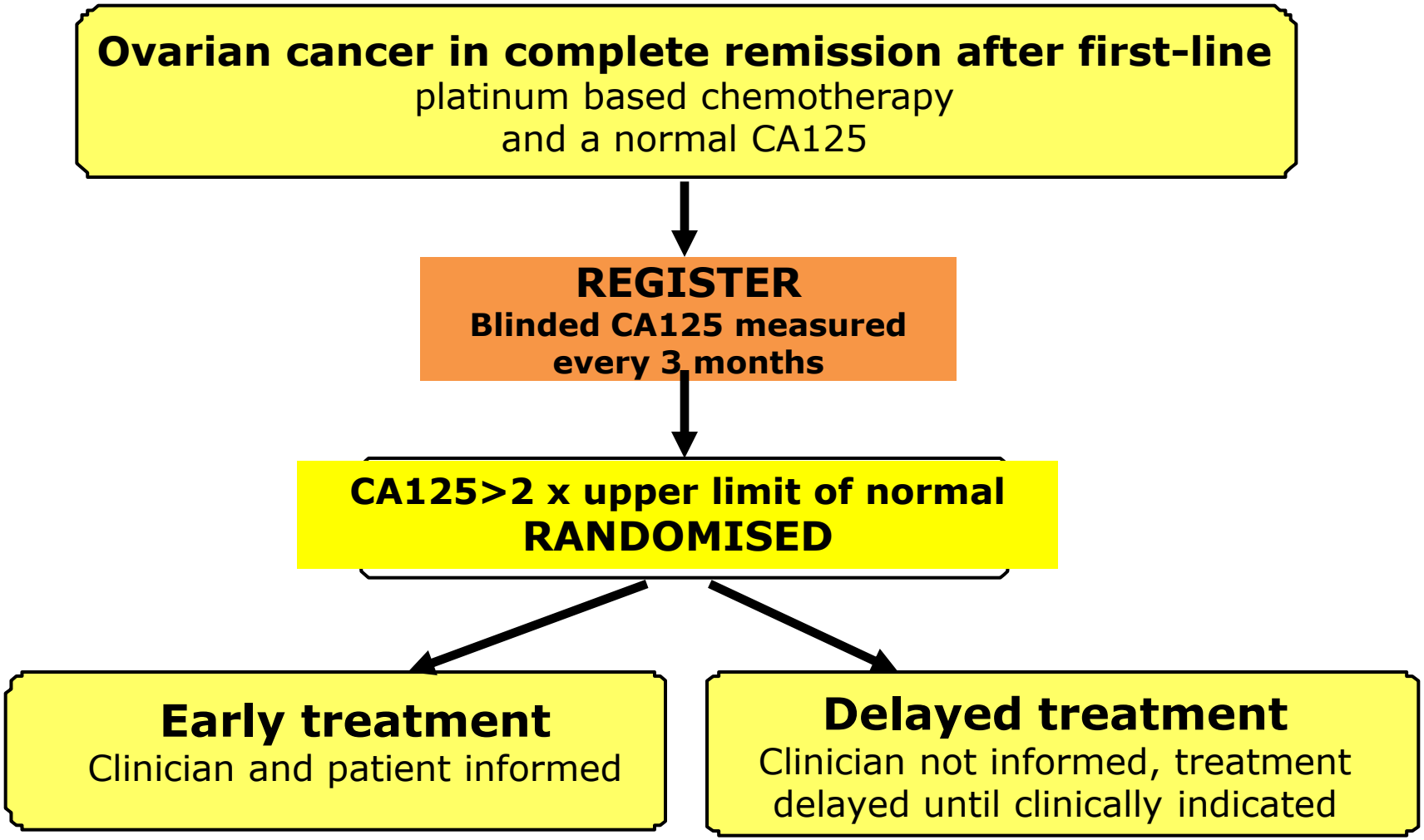
- When CA 125 levels have at least doubled from upper limit of normal or from nadir
  - documented at 2 occasions (> 1 week)
  - Not evaluable if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days

→ The patient was in relapse

Should we treat with chemotherapy a relapse identified by an isolated CA125 level increase ?

NO !

Early treatment based on CA125 level alone vs Delayed treatment



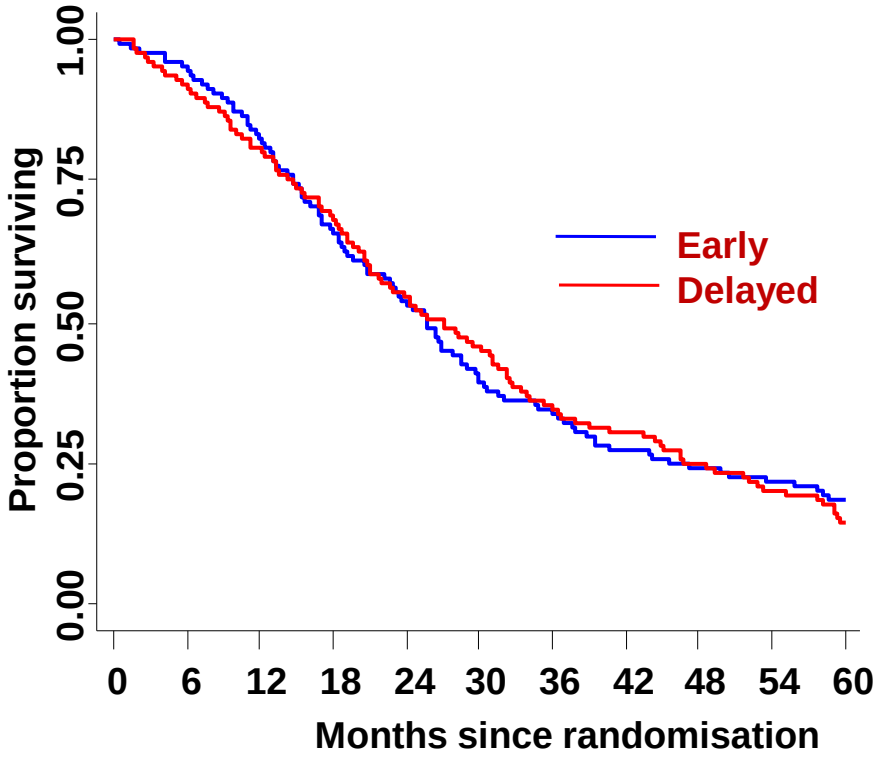
Rustin GJ, et al. Lancet 2010

EORTC European Organisation for Research and Treatment of Cancer

MRC Clinical Trials Unit

Early versus Delayed Chemotherapy

- **Overall survival**



HR=1.00 (95%CI 0.82-1.22) *p=0.98*

- **Overall time spent with 'good' Global Health Score**

	Median (months)	
Early	7.1	
Delayed	9.2	*p=0.15*

Rustin GJ, et al. Lancet 2010

Should I do an imagery when CA125 levels are increasing?

- CT-scan
- PET-CT

  Meta-analysis: PET-CT might be a useful supplement to current surveillance techniques, particularly for those patients with an increasing CA 125 level and negative CT or MR imaging.

Gu P , et al.. CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. .European Journal of Radiology. 71(1):164-74, 2009 Jul.

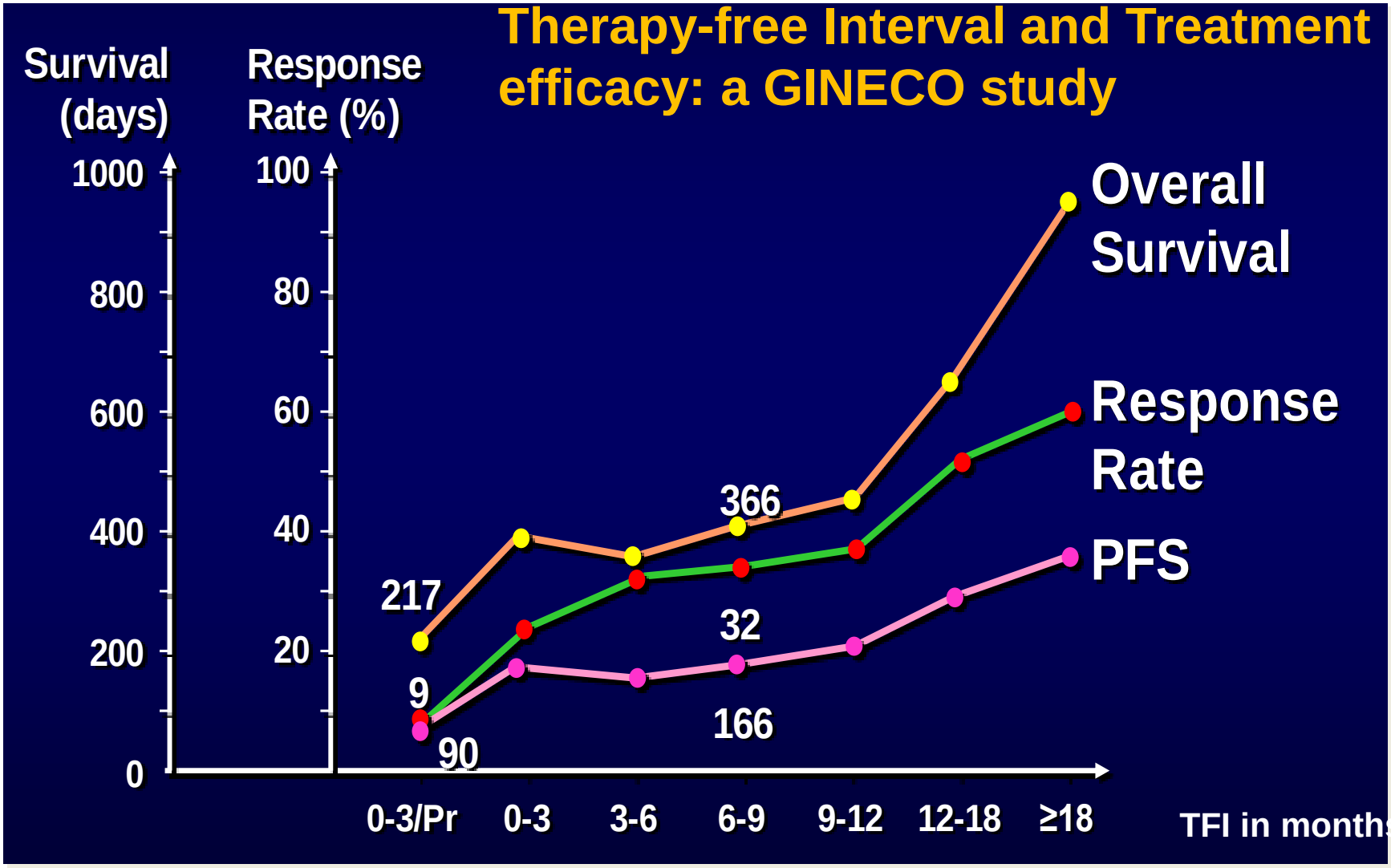
What is the principal predictive and prognostic factor in relapse ?

Recurrent ovarian cancer: population characteristics

4th Ovarian Cancer Consensus Conference
June 25 – 27, 2010
UBC Life Sciences Institute, Vancouver, BC

Platinum-free Interval Interval from last date of platinum dose until progression	Expected platinum sensitivity
Progression while receiving last line of platinum based therapy or within 1 month of last platinum dose	Refractory
1-6 months	Resistant
6–12 months	Partially sensitive
>12 months	Fully sensitive

Disease: Prognostic factors/goals of treatment



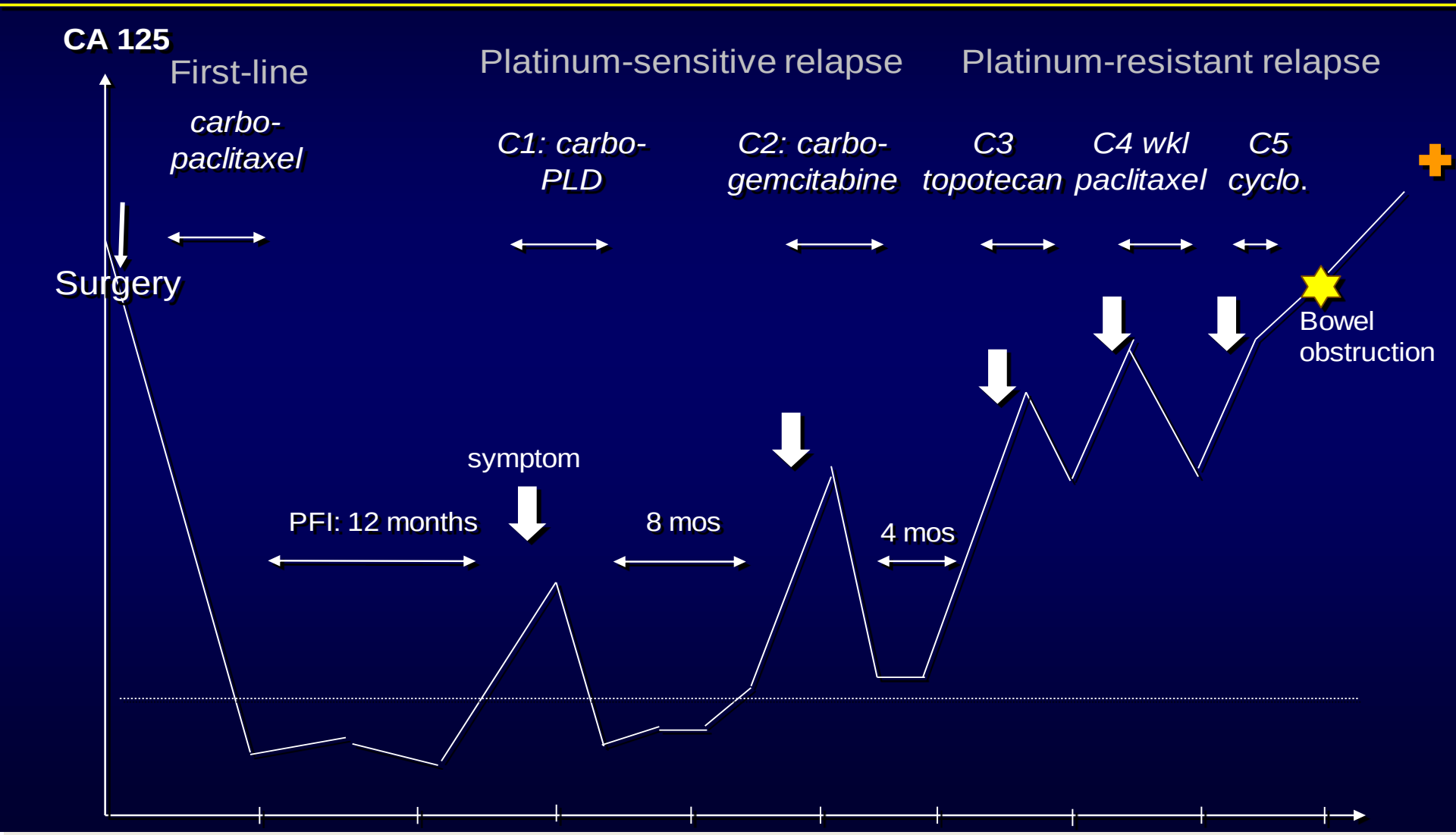
Pujade-Lauraine E, et al. *Proc Am Soc Clin Oncol.* 2002;21: Abstract 829.

Recurrent ovarian cancer: population characteristics

4th Ovarian Cancer Consensus Conference
June 25 – 27, 2010
UBC Life Sciences Institute, Vancouver, BC

- ✓ **Each trial will need to specify how they define the date of progression (Ca-125 alone, radiological, symptomatic).**
- ✓ **Document whether patient had maintenance/ consolidation therapy – which agent and for how long.**
- ✓ **Document histological subtype, molecular markers (such as BRCA), and surgery for recurrent disease.**

Advanced ovarian cancer : a « chronic » disease with multiple relapses



PFI: platinum-free interval or duration of disease control without chemotherapy

Carbo: carboplatin, PLD: pegylated liposomal doxorubicin,wkl paclitaxel: weekly paclitaxel Cyclo: cyclophosphamide

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		
PFS		
Survival		

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

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

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

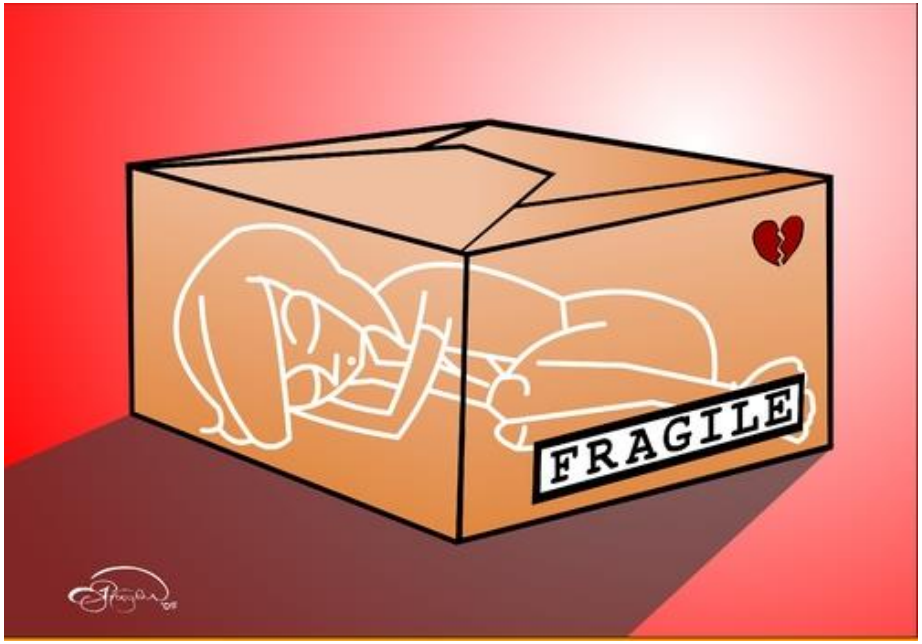
Gynecologist German Survey n = 327

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

Personalized treatment:
which patient characteristics are important to take into consideration?

Choice depends on

- **Patient predicted fragility**
  - **Age**
  - **Performans status**
  - **Depressive state**
  - **Comorbidities**

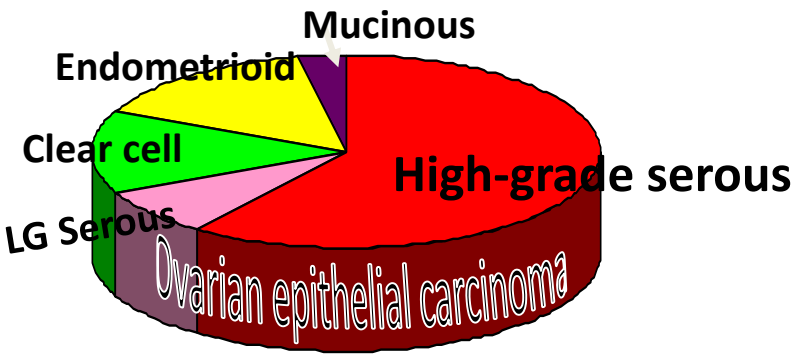


Choice depends on

- **Toxicity from prior therapy**
  - **Neurotoxicity**
  - **Hematotoxicity**
  - **Hypersentivity to previous drug**

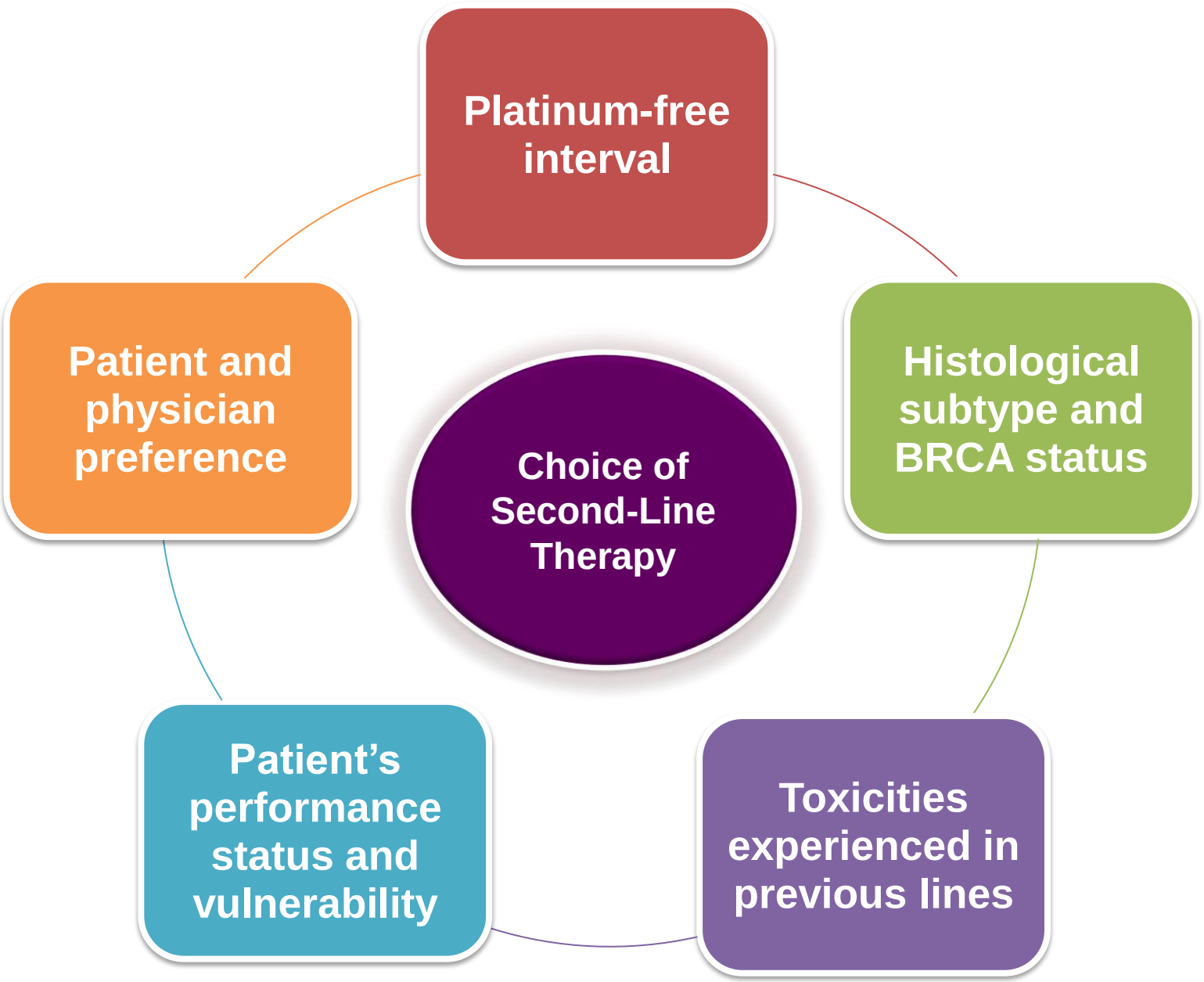
Choice depends on

- **Histologic subtype and grade**
  - **Serous low grade**
  - **Mucinous**
  - **Clear cell**
- **BRCA1 et BRCA2 mutation**

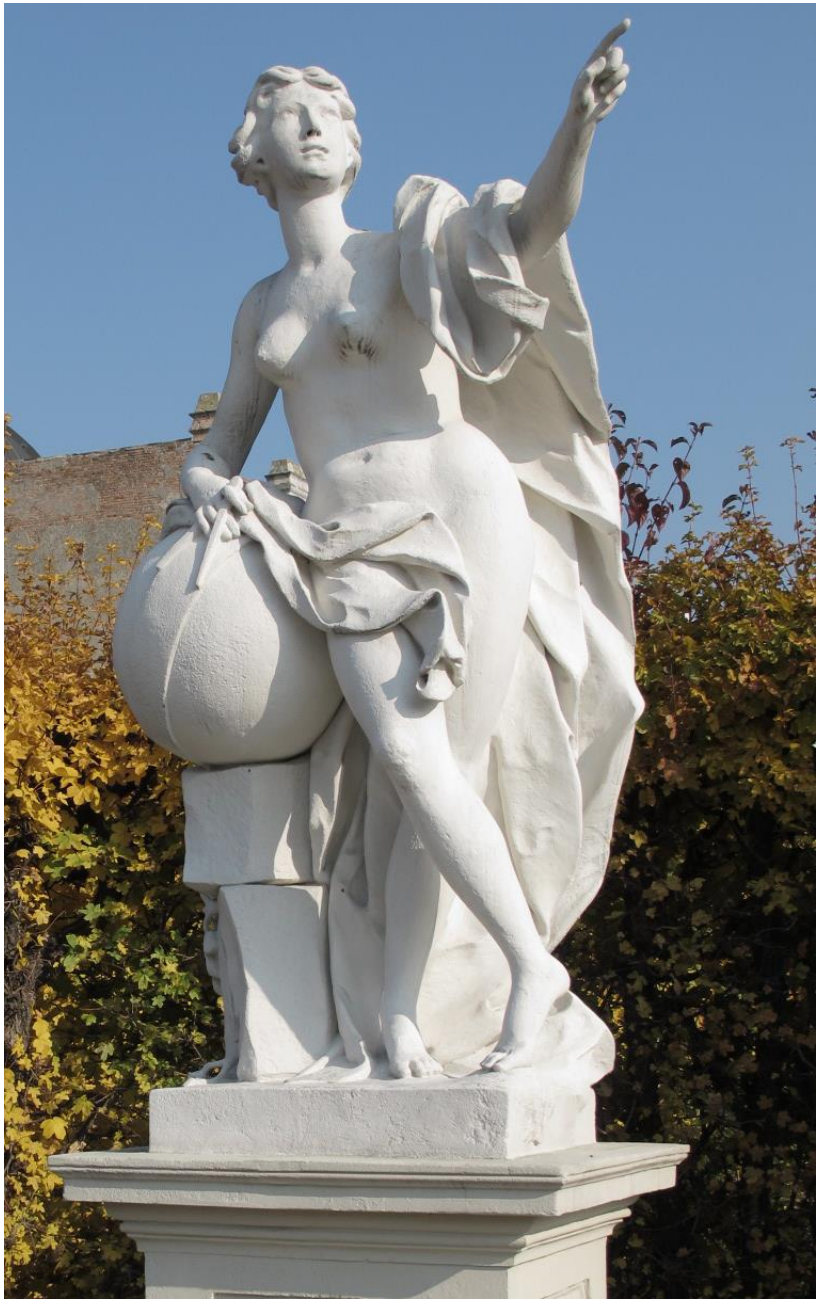


Choice depends on

- **Patient wish**
  - **Avoid alopecia**
  - **One day vs multiday infusion/course**


Platinum-free interval
Histological subtype and BRCA status
Toxicities experienced in previous lines
Patient's performance status and vulnerability
Patient and physician preference
Choice of Second-Line Therapy

Platinum-resistant relapse



A 59 yr old woman is recurring 4 months after the last cycle of platinum.

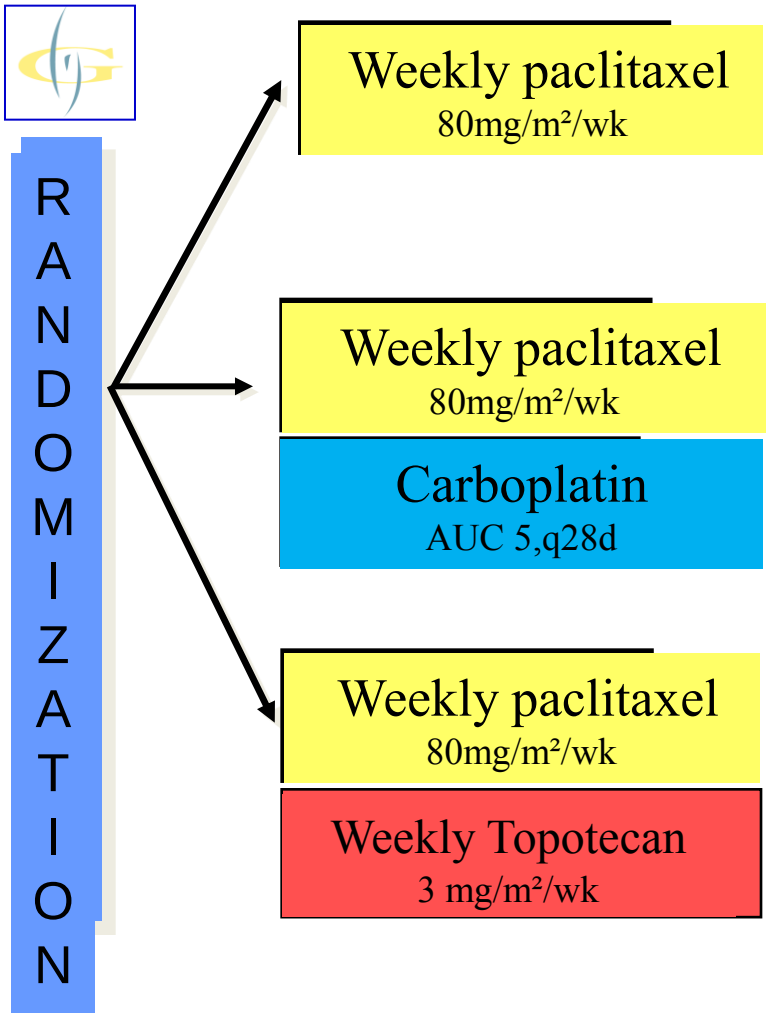
Would you offer this patient a combination chemotherapy?

- **yes**
- **no**

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 + trabectidin	Monk et al, 2010	No
Weekly paclitaxel (wP) vs wP + carboplatin or weekly topotecan (CARTAXHY)	Gladieff et al, 2009	No

Resistant Relapse: single agent versus doublet - GINECO trial



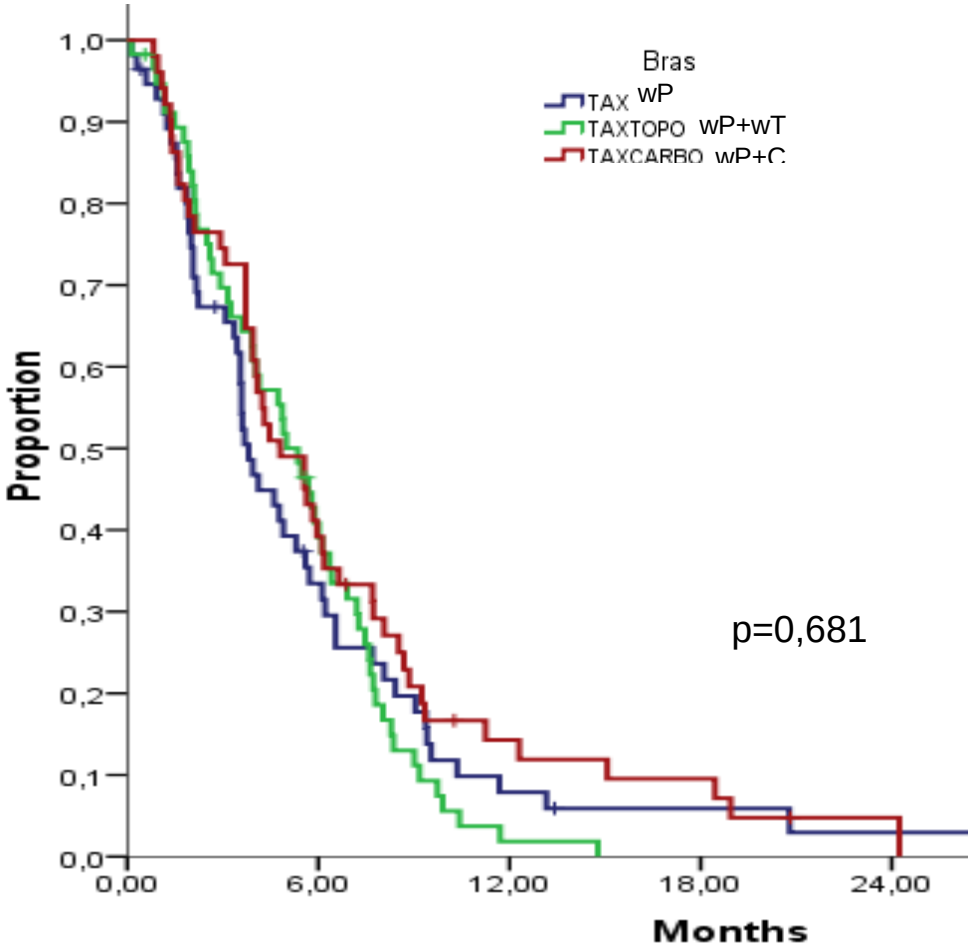
Lortholary A, et al. Ann Oncol 2012

Response rate (% of patients)

	wP (N=57)	wP+Cb (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**
Non evaluable	**15,8**	**7,8**	**14**

Lortholary A, et al. Ann Oncol 2012

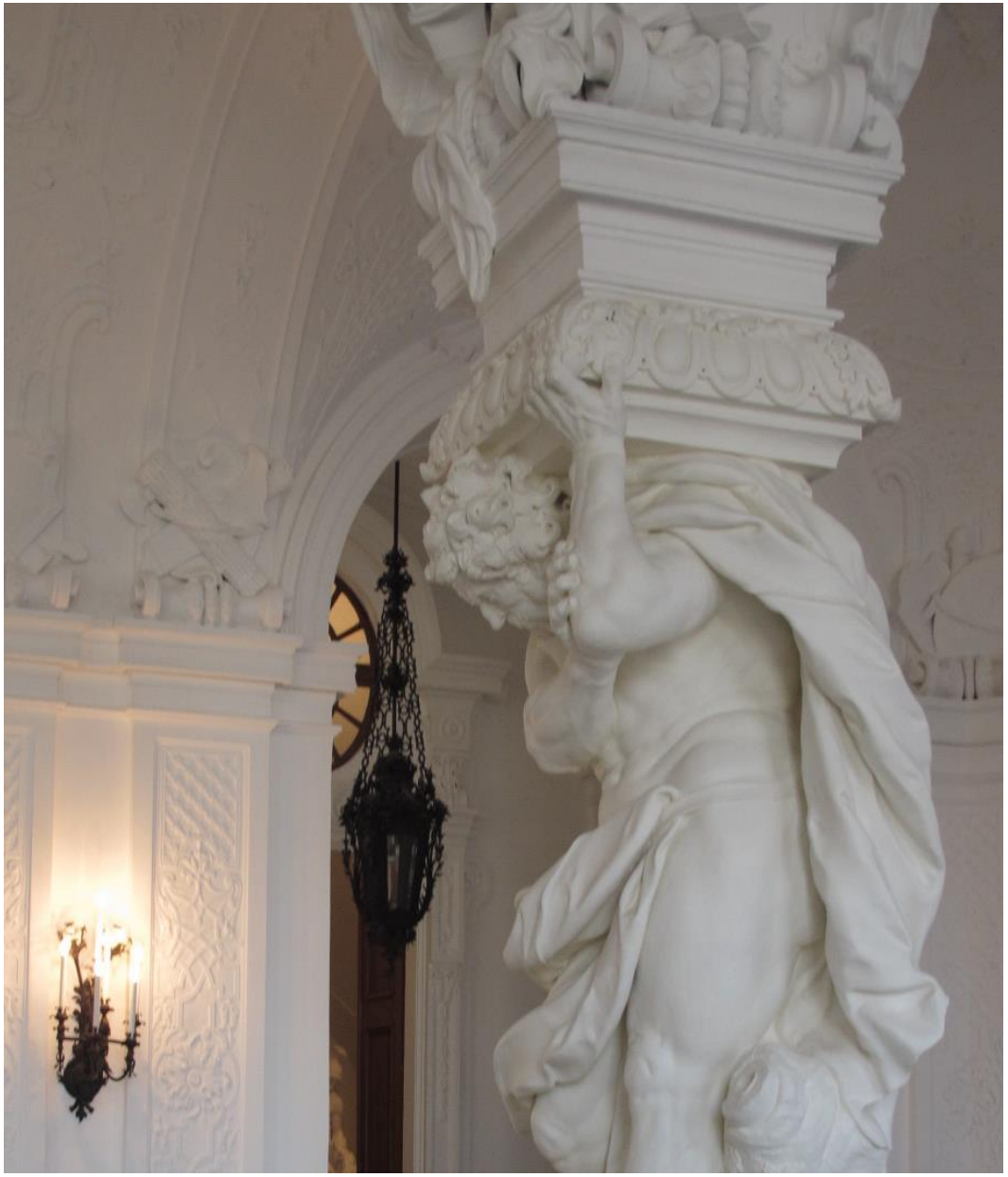
Single agent versus doublet - GINECO trial- PFS results



Lortholary A, et al. Ann Oncol 2012

Chemoresistant Relapse: Principles

- ***Single-agent regimens***
- **Drugs active in resistant disease (no platinum)**
- **Sequential use of agents with goal of palliation and disease control**



What is your preferred option in patients with resistant disease ?

- **alkykating agent**
- **topotecan**
- **weekly paclitaxel**
- **Caelyx**
- **others**

Resistant Disease: Available Agents

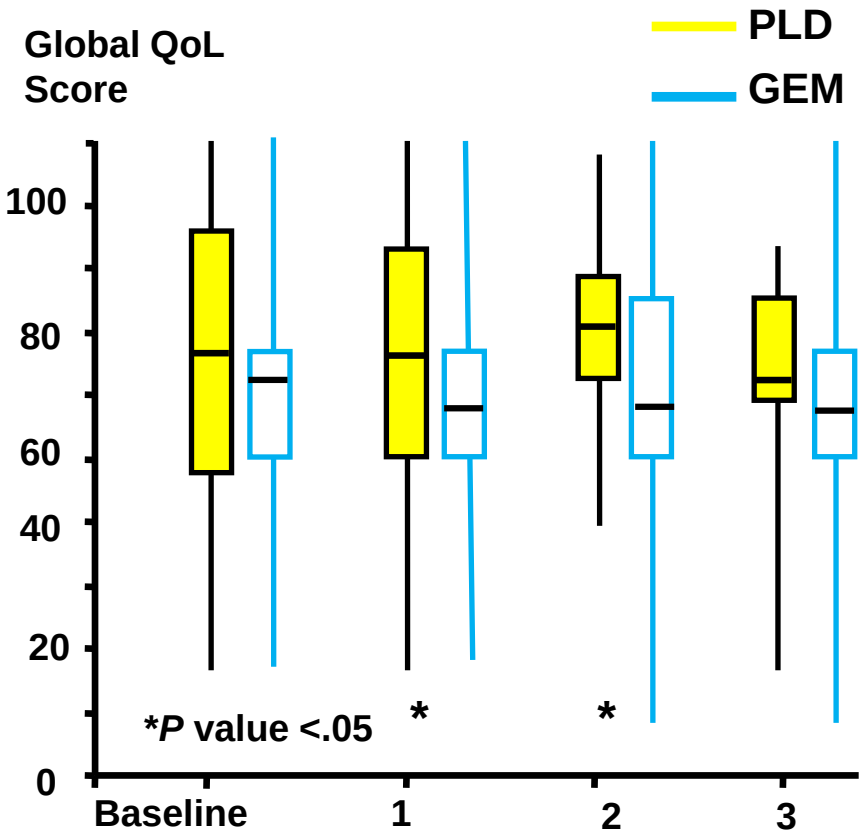
Agent	No. of Patients	Response Rate
PLD (Caelyx)	428	18%
Topotecan	882	17%
Paclitaxel	1580	22%
Oral etoposide	234	31%
Gemcitabine	181	18%
Hexamethylmelamine	235	18%
Oxaliplatin	118	23%
Vinorelbine	71	23%

PLD = Pegylated liposomal doxorubicin

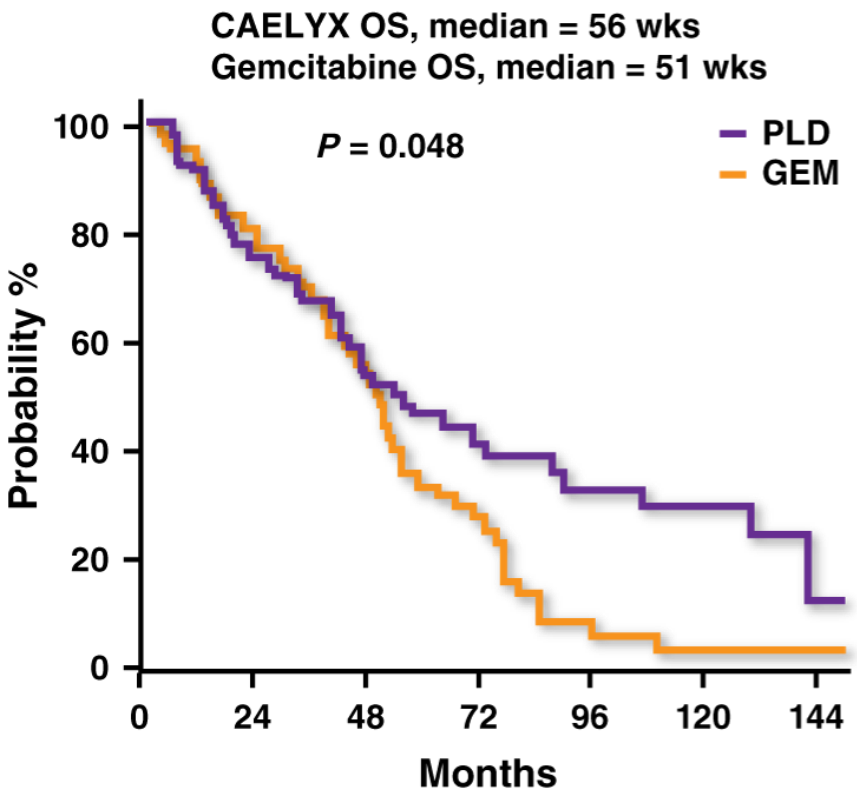
Gore M. ASCO Education Booklet. 2001.

CAELYX vs Gemcitabine in ROC:
Outcomes

Global QoL score

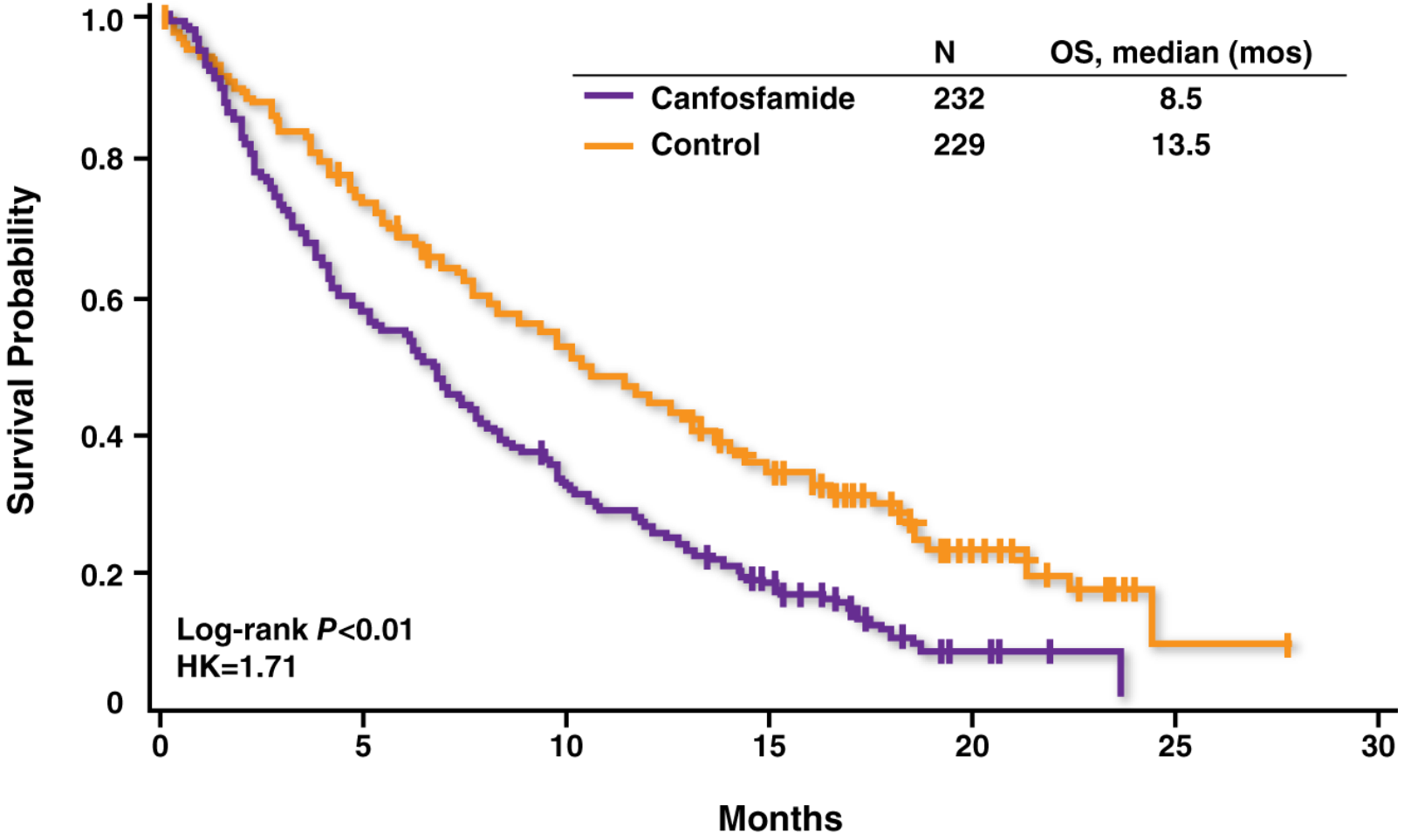


Overall Survival



Ferrandina et al. J Clin Oncol. 2008;26:890-896.

Canfosfamide vs CAELYX or Topotecan:
Overall Survival



- **Platinum-resistant or refractory disease (1st-line platinum pre-treated patients) and had failed or progressed after 2nd-line therapy with CAELYX or topotecan**

Vergote et al. Eur J Cancer. 2009;45:2324-2332.

Platinum-sensitive relapse
(PFI > 6 months)

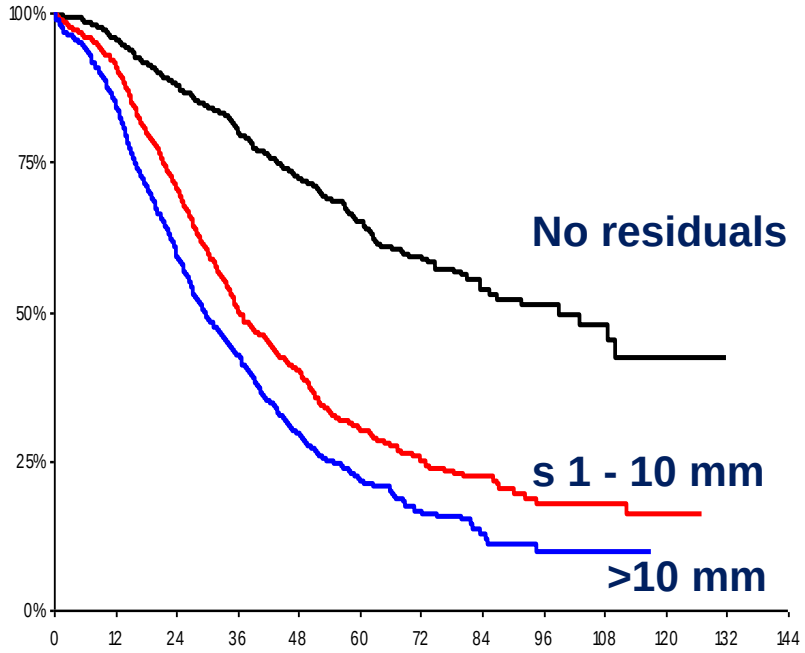
A 59 year old patient is recurring 18 months after the last platinum- cycle PS=0. CT-scan: no ascites, one pelvic mass (42 mm) and one LA lymph node (23 mm).

Would you discuss a new surgery?

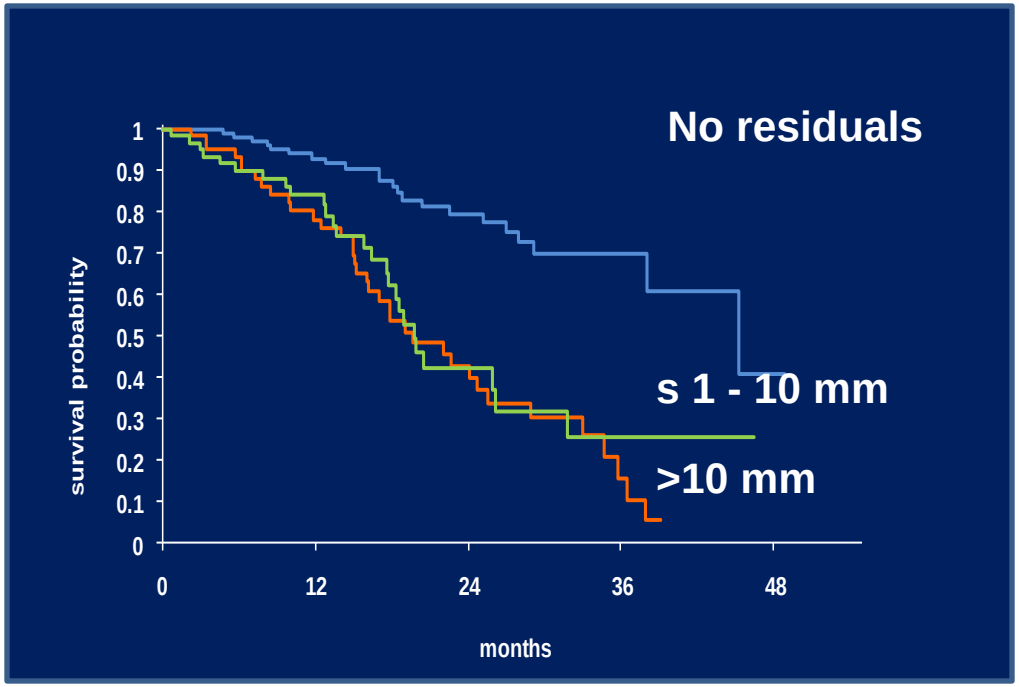
- **yes**
- **no**

DESKTOP-1: Surgical Endpoint of surgery at relapse

Initial surgery



Surgery at relapse



AGO-OVAR

Harter P, et al. Ann Surg Oncol 2009

DESKTOP-1: predictor of complete resection- Multivariate Analysis

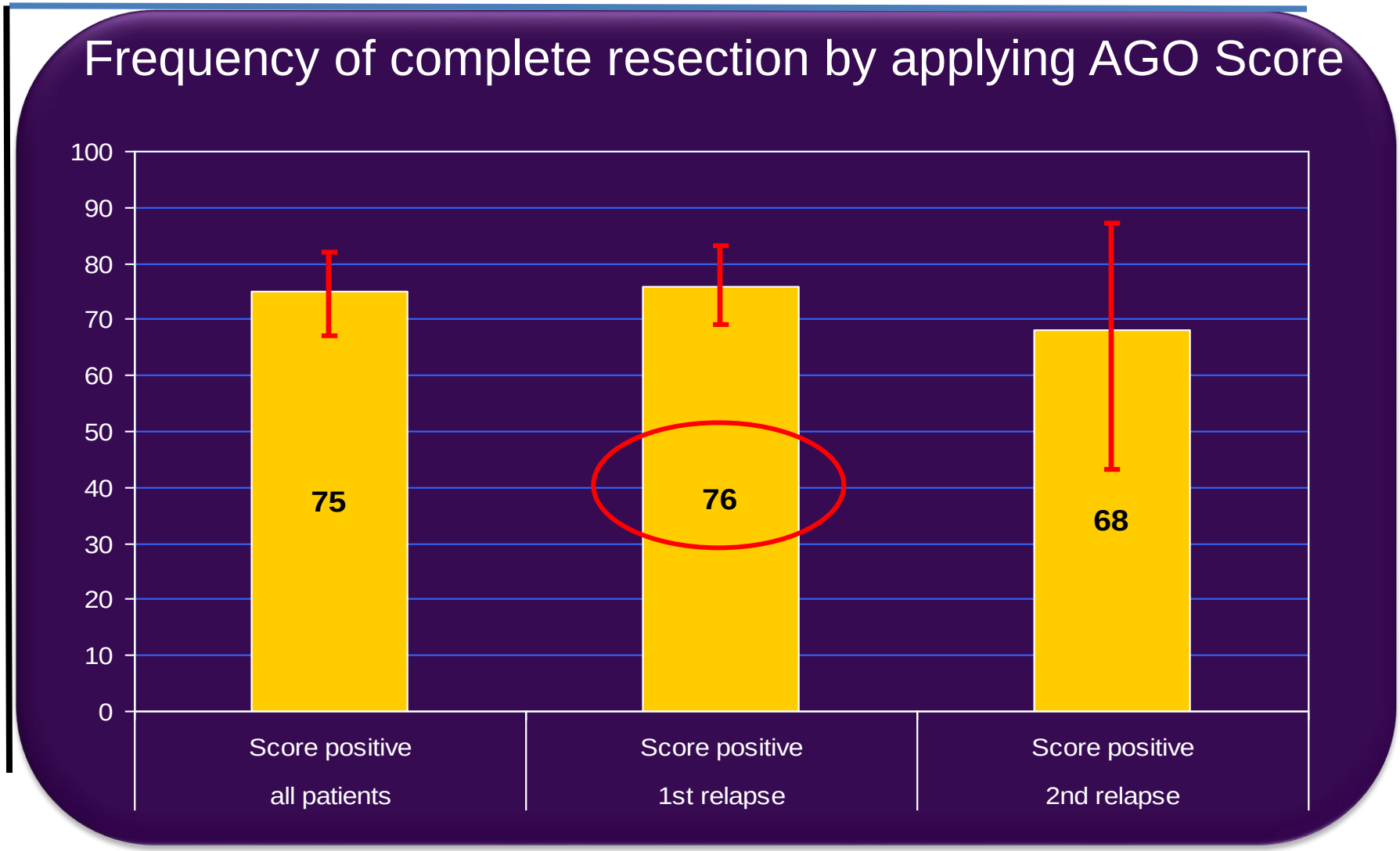
Variables		HR (95% CI)	P-value
PS ECOG	0 > 0	1 2.56 (1.49 – 4.42)	< .001
Residual disease (after 1st surgery)	0 mm > 0 mm	1 2.09 (1.20 – 3.64)	.009
Ascites (cut-off 500 ml)	< 500 ml ≥ 500 ml	1 4.26 (1.62 – 11.24)	.003

* ***Initial FIGO-stage I/II vs III/IV*** *alternatively, if residual disease after 1st surgery is unknown*

AGO-OVAR

Harter P, et al. Ann Surg Oncol 2009

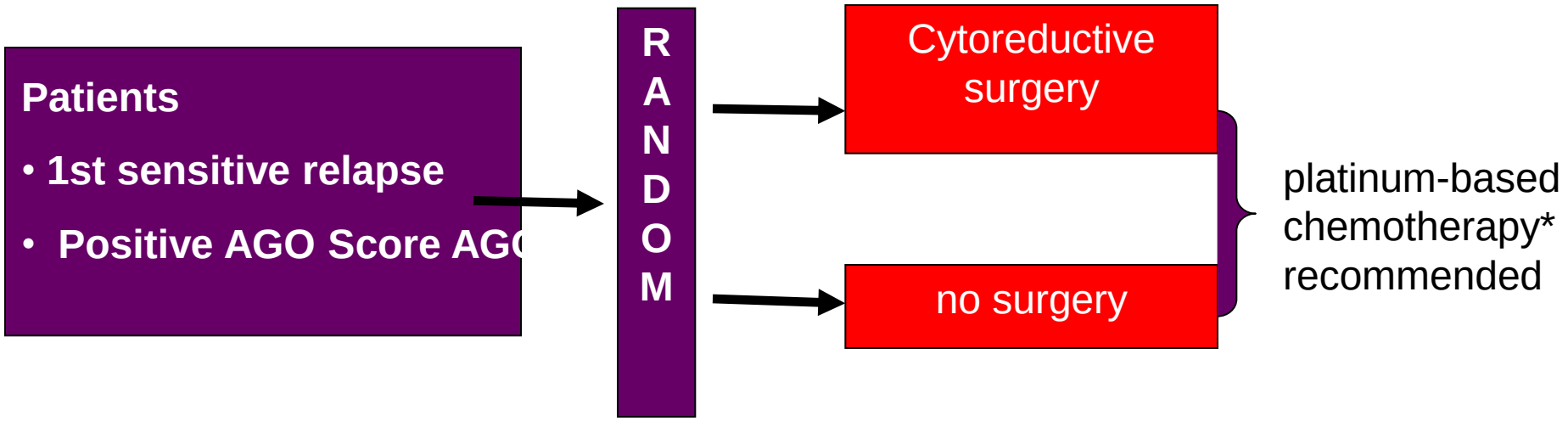
DESKTOP-2: Surgical results



Harter P, et al. Int J Gynecol **Cancer**. 2011

AGO-OVAR DESKTOP III

A randomized trial evaluating cytoreductive surgery
in patients with platinum-sensitive recurrent ovarian cancer



Primary objective : overall survival

* Recommended platinum-based chemotherapy regimens:
- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin
-or other platinum combinations in prospective trials

She had surgery with again a complete macroscopic resection.

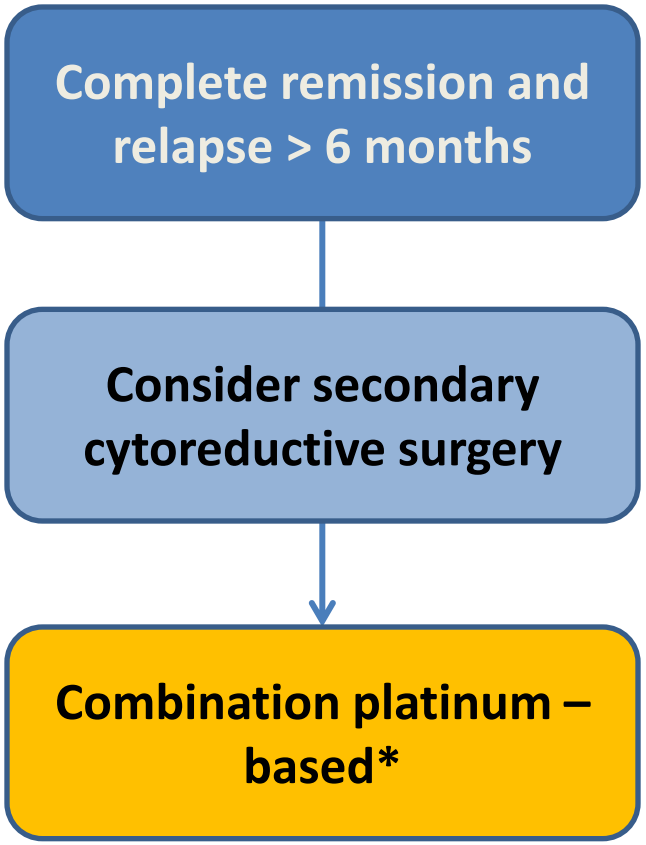
Would you offer this patient a combination chemotherapy or single agent ?

Carboplatin (Cb) combo vs Cb alone in platinum-sensitive recurrent OC

Experimental arm	Group/ author	Difference in PFS	Difference in OS
Carboplatin +			
paclitaxel	**ICON4/ AGO 2.2**	**Yes**	**Yes**
paclitaxel	**GEICO** Gonzales-Martin	**Yes**	**Yes**
gemcitabine	**AGO/GCIG** Pfisterer	**Yes**	**No**
PLD	**Alberts**	**No**	**Yes**

PLD: pegylated liposomal doxorubicin

Current treatment recommendations for platinum-sensitive disease



* Preferred for 1st line recurrence

NCCN. Clinical Practice Guidelines in Oncology. Ovarian Cancer v.2.2010

- A platinum-based combination therapy should be the control arm for randomized trials in patients with progression-free interval since last line of platinum of >12 mo

Carboplatin-paclitaxel rechallenge (ICON4) toxicity

	Plat (n = 410)	Pac-Plat (n = 392)
Neurological (grade ≥2)	1%	20%
Mucositis (grade ≥2)	6%	7%
Nausea and vomiting (grade ≥2)	40%	35%
Alopecia (grade ≥2)	25%	86%
Haematological*	46%	29%
Infection*	14%	17%
Renal*	9%	8%

* toxicity not graded, but led to treatment modification or interruption

Parmar PK et al, Lancet 2003

Carboplatin-gemcitabine (GCIG trial) hematologic toxicity

	Gem/Carbo	Carbo	p-value
Grade 3+4 (% of pts)	78.3	24.7	< 0.001
Anemia	27.4	8.0	< 0.001
Thrombocytopenia	34.9	11.5	< 0.001
Neutropenia	70.3	12.1	< 0.001
Febrile Neutropenia	1.1	0.0	n.s.
Infections	0.6	0.6	n.s.
G(M)-CSF	23.6	10.1	< 0.001
Parenteral Antibiotics	8.4	5.1	n.s.
RBC	27.0	6.7	< 0.001

Pfisterer J et al, J Clin Oncol 2006

Carboplatin-topotecan (HECTOR)

RANDOMISATION

Topotecan **0.75 mg/m²** **d 1-3**
Carboplatin AUC 5 d 3 q21d

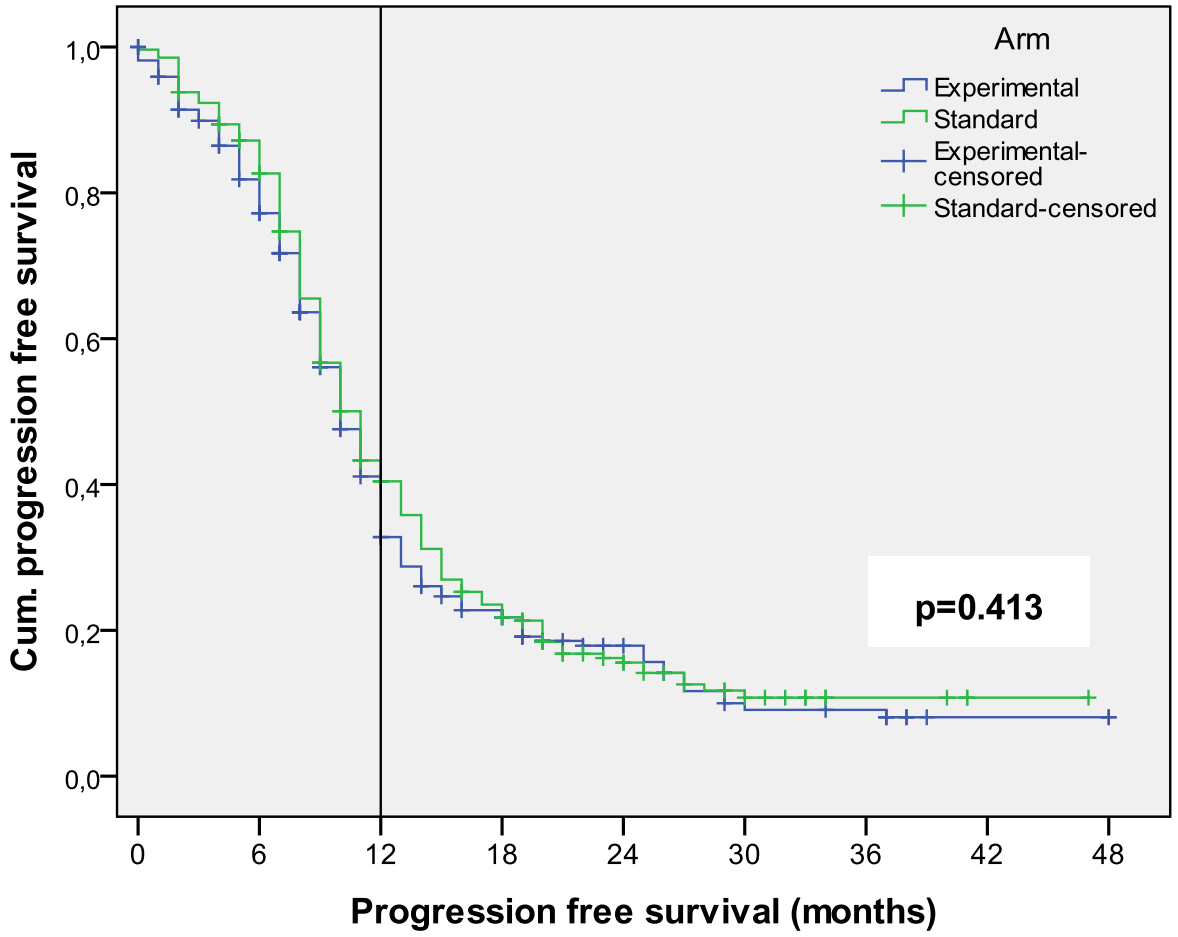
Paclitaxel 175 mg/m²
Carboplatin AUC 5 q21d

or

Gemcitabine 1g/m² d 1+8
Carboplatin AUC 4 q21d

Sehouli J et al, ASCO 2012

Progression-free survival



Sehouli J et al, ASCO 2012

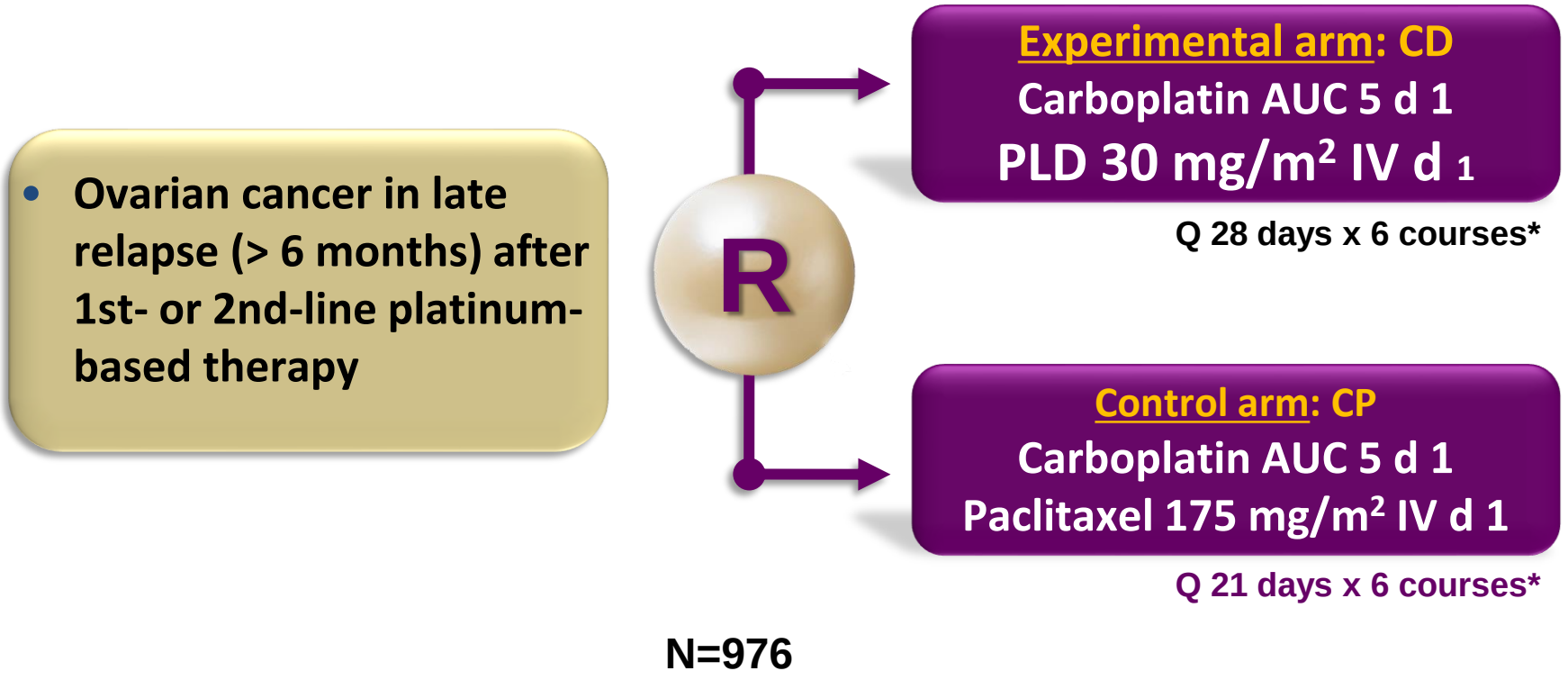
Toxicity

Toxicity (%)	Carbo + TOPOTECAN (n=270)	Carbo+ PACLITAXEL (n=79)	Carbo+ GEM (n=189)	p-value
Anaemia G 3/4	10.7	5.1	13.2	
Thrombocytopenia G 3/4	15.2	3.8	41.8	<0.001
Neutropenia G3/4	27.8	34.2	40.7	0.015
Alopecia ≥ G2	4.8	62.0	12.7	<0.001
Neuropathy ≥ G2	10.8	17.7	8.5	0.073
Hypersensitivity ≥ G2	15.2	12.7	8.5	0.100
Early TT termination (toxicity related <6 cy)	15.9	7.6	13.2	0.162

GCIG Intergroup CALYPSO Trial

Design

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

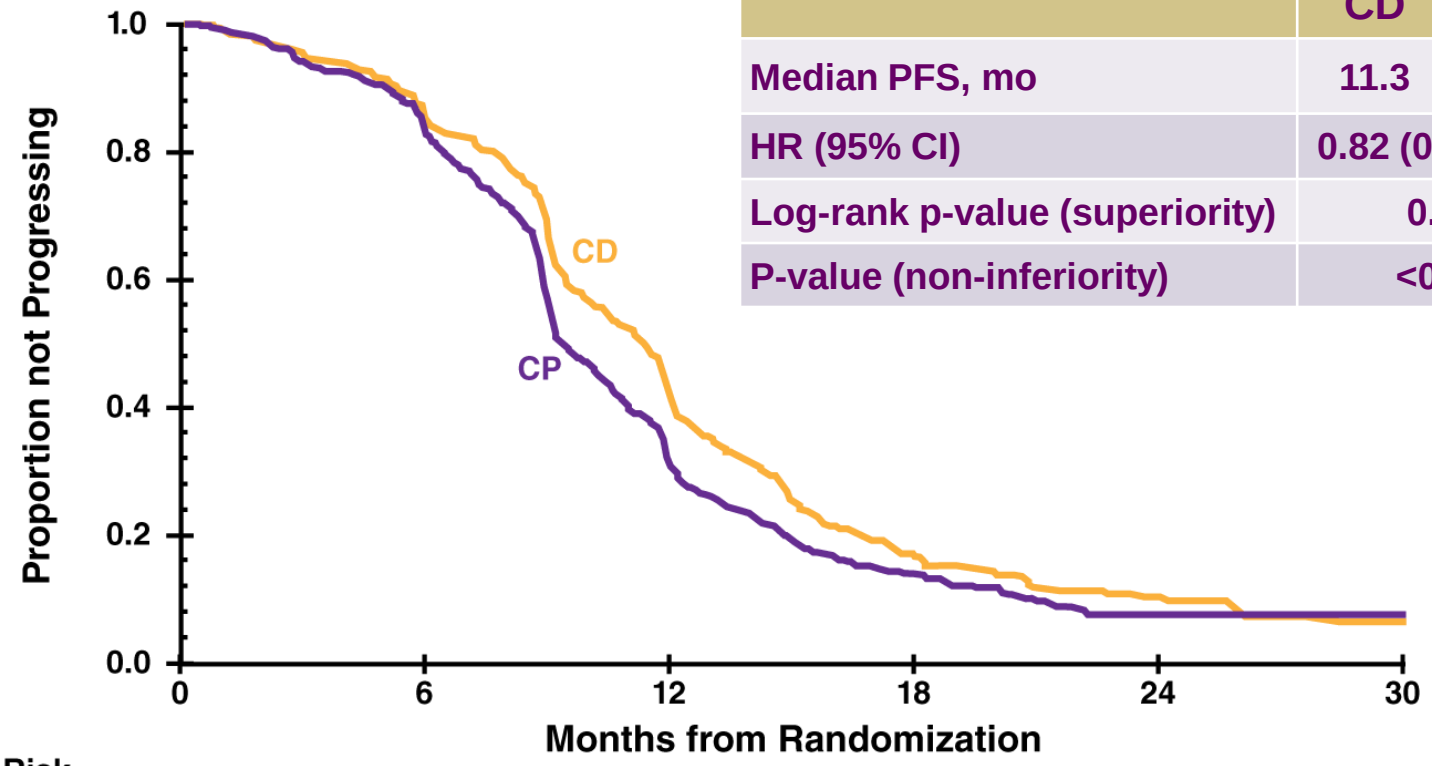


N=976

Pujade-Lauraine E, et al. J Clin Oncol.2010. .

CALYPSO
Progression-Free Survival (ITT)

Median follow-up: 22 months
Number of events: 824 (85%)



	CD	CP
Median PFS, mo	11.3	9.4
HR (95% CI)	0.82 (0.72, 0.94)	
Log-rank p-value (superiority)	0.005	
P-value (non-inferiority)	<0.001	

Number at Risk

CD	467	397	188	60	20	4
CP	509	405	152	45	10	2

Pujade-Lauraine E, et al. J Clin Oncol.2010.

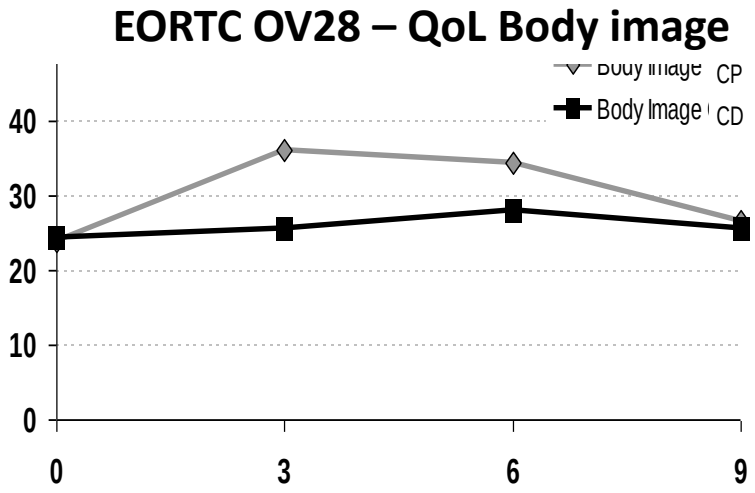
Alopecia: Carboplatin-PLD is preferred to Cb-paclitaxel

CALYPSO trial

	CD (n=466)		CP (n=501)	
	Grade 2	Grade 3/5	Grade 2	Grade 3/5
Alopecia*	**7%**		**84%**	

****P< 0.001***

Body image score over time



Brundage M, Gropp M, Mefti K et al. Ann Oncol. 2012 Jan 30.

Neurotoxicity and Allergic Reactions as a funtion of age

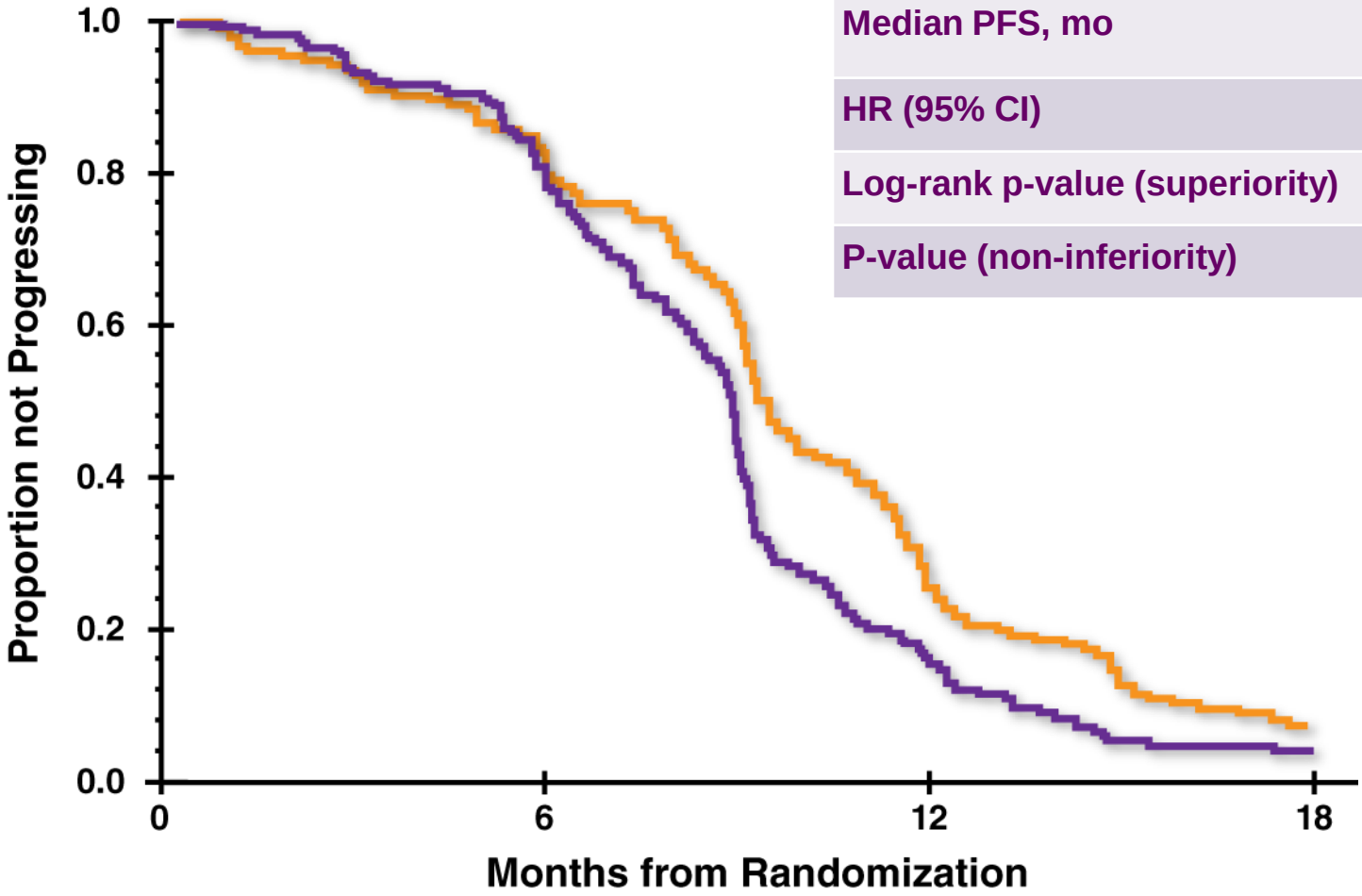
toxicity	<70 yrs	Elderly ≥ 70 yrs		
	Whole population	Whole population	Treated with	
			Cb-PLD	Cb-Paclitaxel
Neuro Gr2/3	16%	24%*	10%	36%*
Allergic reaction Gr2/3	14%	6%*	4%	7%

**P< 0.01*

Kurtz JE, et al. Ann Oncol. 2011 Nov;22

CALYPSO Subgroup Analysis:
*PFS in **Partially** Platinum Sensitive Population*

	CD N= 165	CP N= 183
Median PFS, mo	9.4	8.8
HR (95% CI)	0.73 (0.58, 0.90)	
Log-rank p-value (superiority)	0.004	
P-value (non-inferiority)	<0.001	



Vasey P, et al. ECCO 15 and 34th ESMO Multidisciplinary Congress. 2009 Late-breaking Abstract 18.

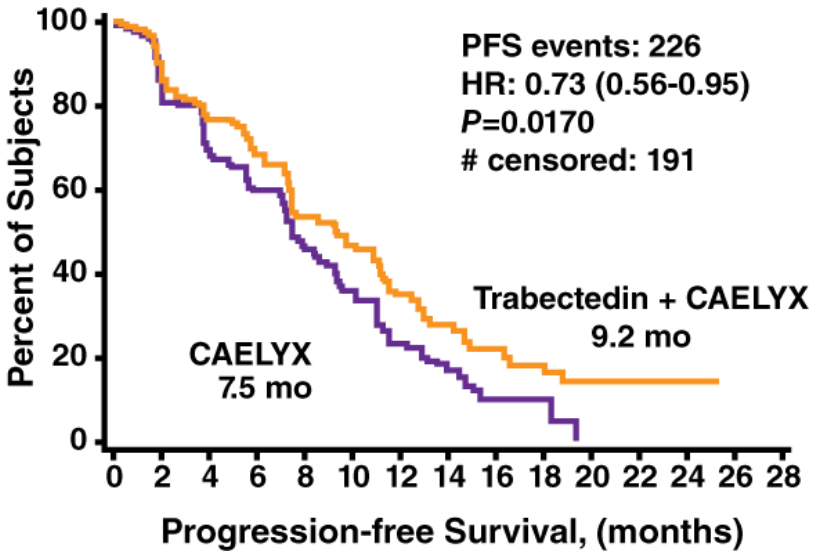
Trabectedin +PLD

OVA-301 TRIAL (N=672)

R

- **PLD**50mg/m² every 4 weeks
- **PLD** 30mg/m², 3h
- **Trabectedin** 1,1 mg/m², 3 h every 3 weeks

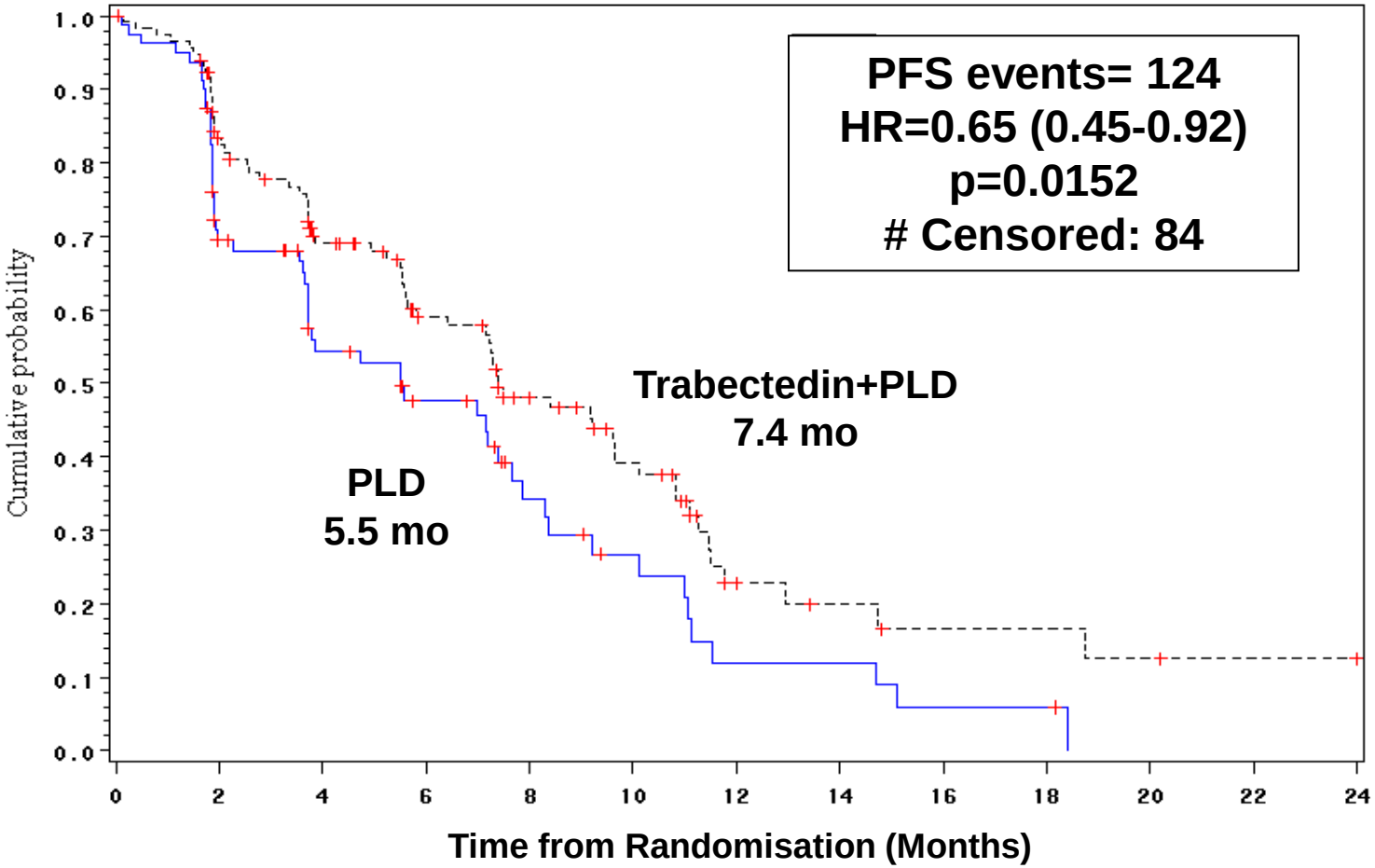
PFS in patients relapsing > 6 months



Monk et al. J Clin Oncol 2010; 28(19):3107-14

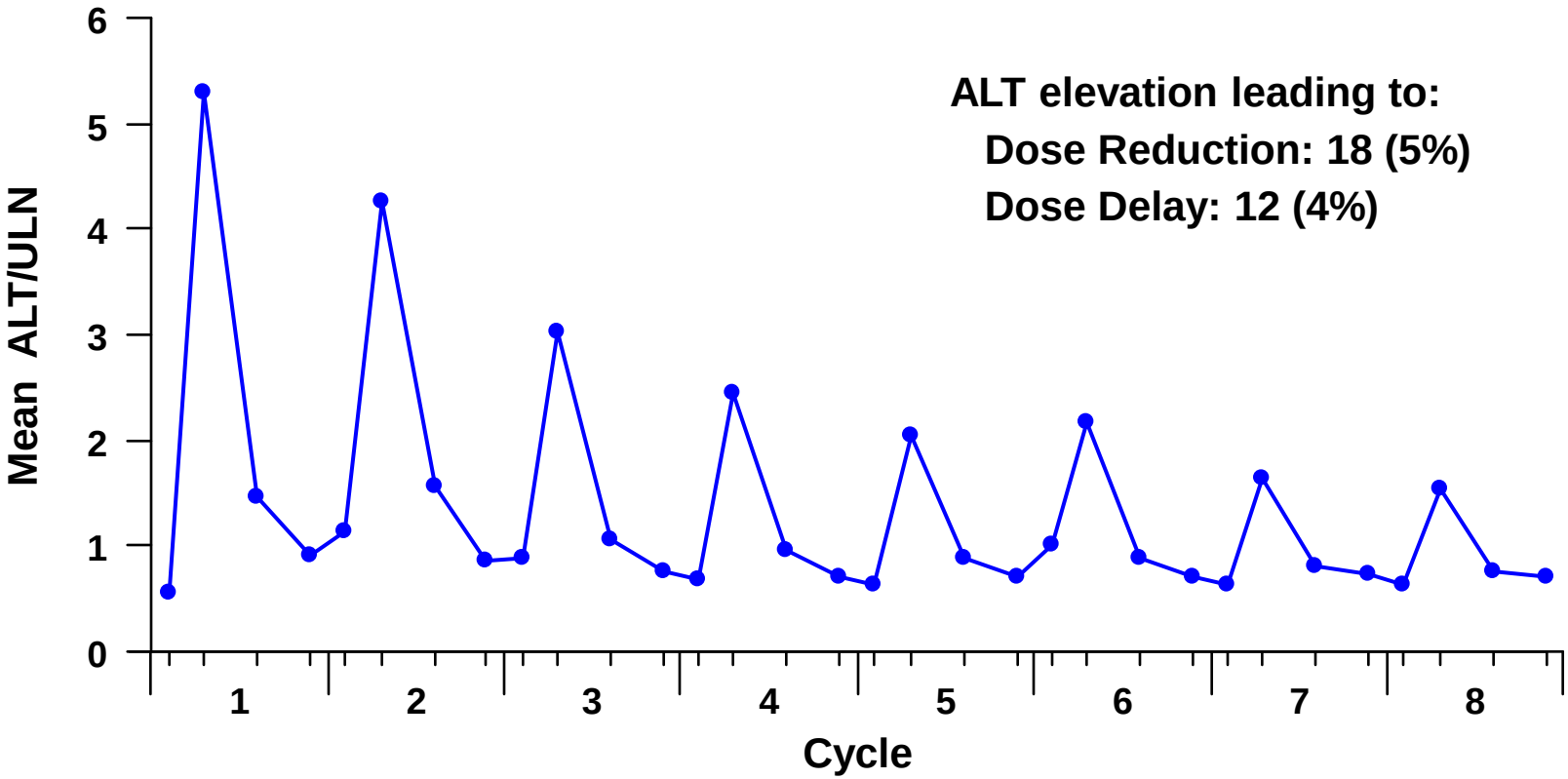
PFS – Intermediate Sensitivity (PFI 6-12 mo)

Independent Radiology (n=208)



PFI = Platinum Free Interval

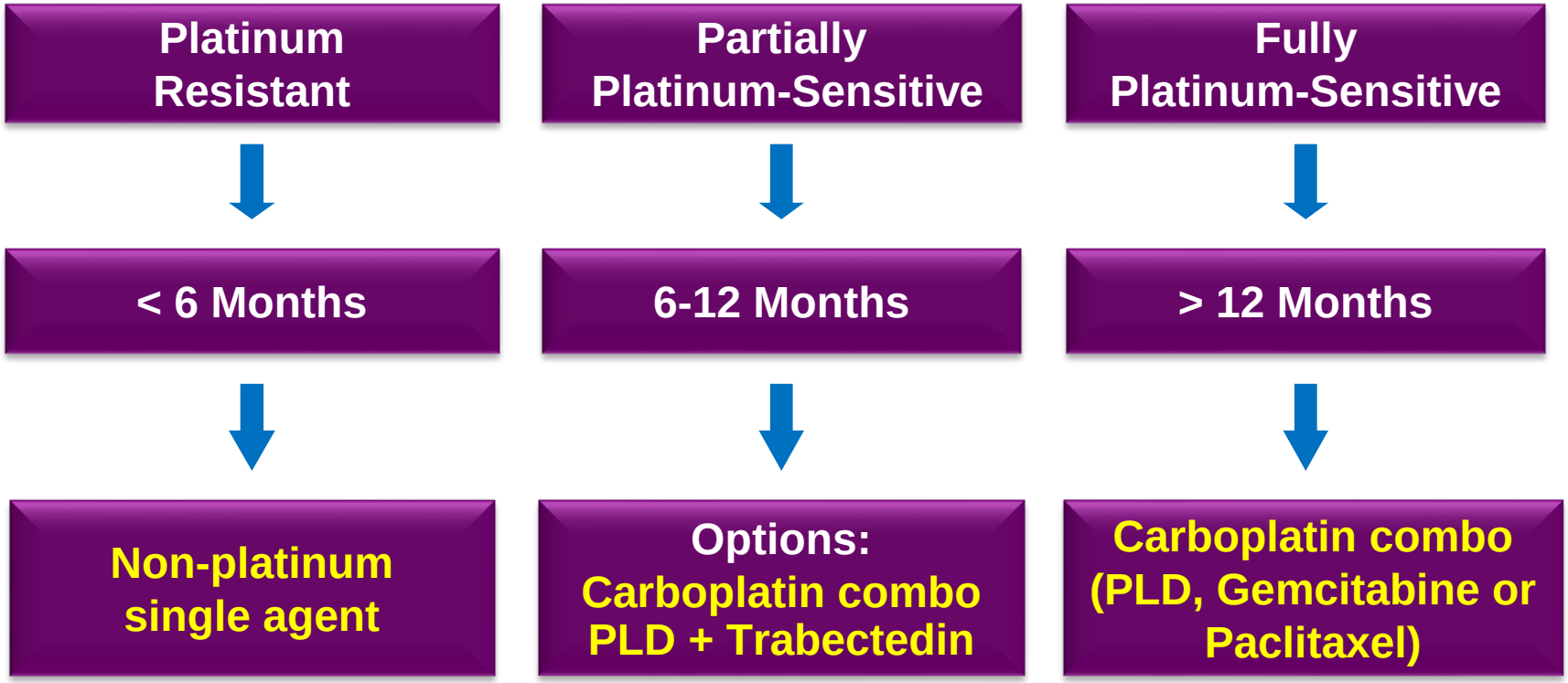
Mean ALT Among All Patients During Treatment With Trabectedin + PLD



Progression-free survival in phase III trials (6-12 months)

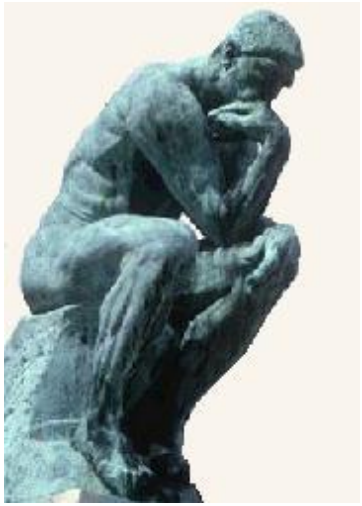
Treatment	Group/Name	Median PFS, mo
Carboplatin-PLD	CALYPSO	9.4
Carboplatin-paclitaxel	CALYPSO	8.8
Carboplatin-gemcitabin	AGO-GCIG	7.9
Trabectedin-PLD	OVA-301	7.4
PLD	OVA-301	5.5
Carboplatin	AGO-GCIG	5.2

Generally Accepted Guideline for Chemotherapy at Recurrence

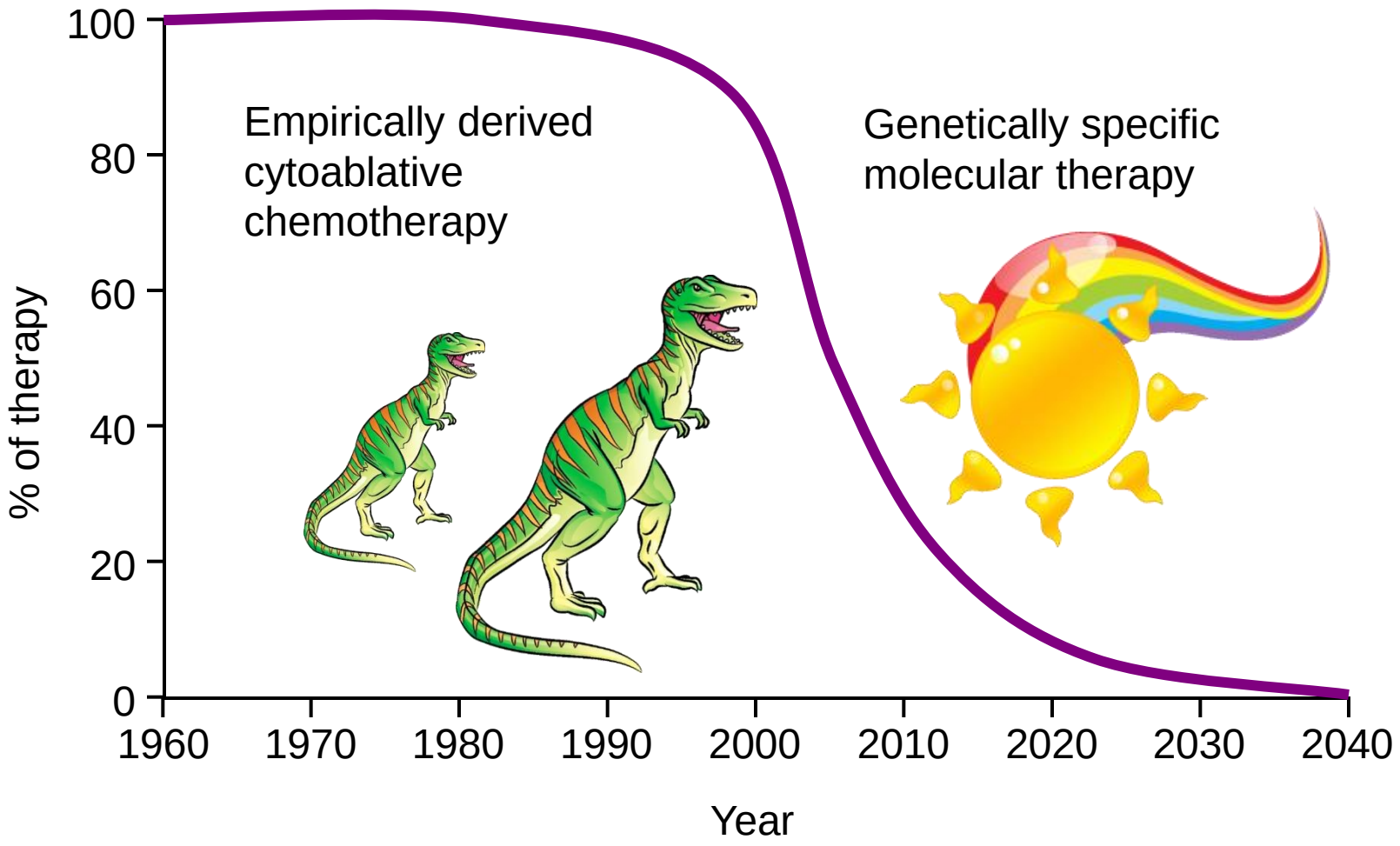


Choice of treatment in platinum-sensitive disease

CHOICE



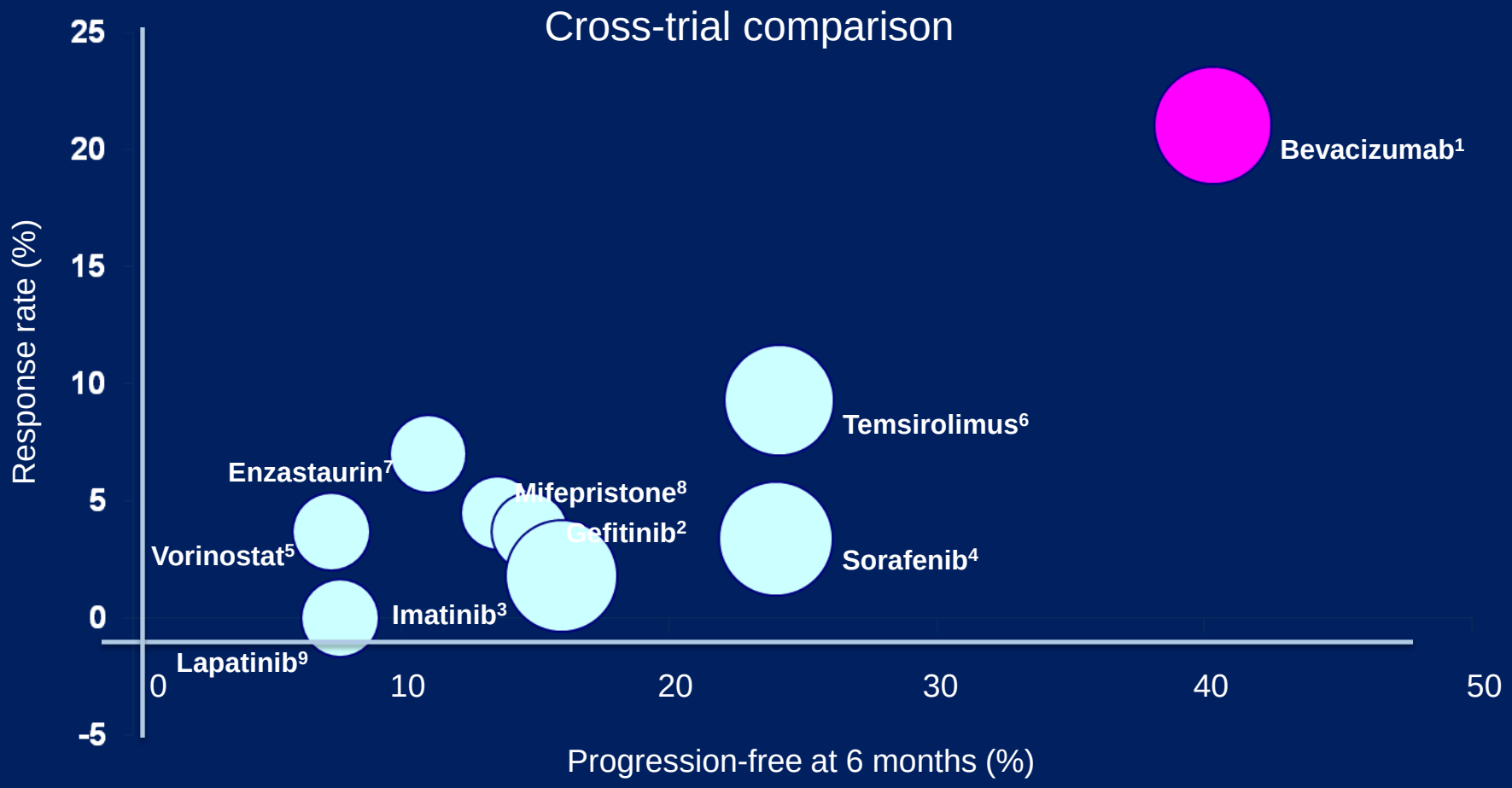
- Drug availibility?



From Edmonson JH. *Gynecol Oncol* 2000; 79:145–146

Anti-angiogenic agents

Targeted therapy GOG phase II



Bevacizumab phase III results in recurrent ovarian cancer

Recurrent

AURELIA
Avastin Use in Platinum-resistant Epithelial Ovarian Cancer

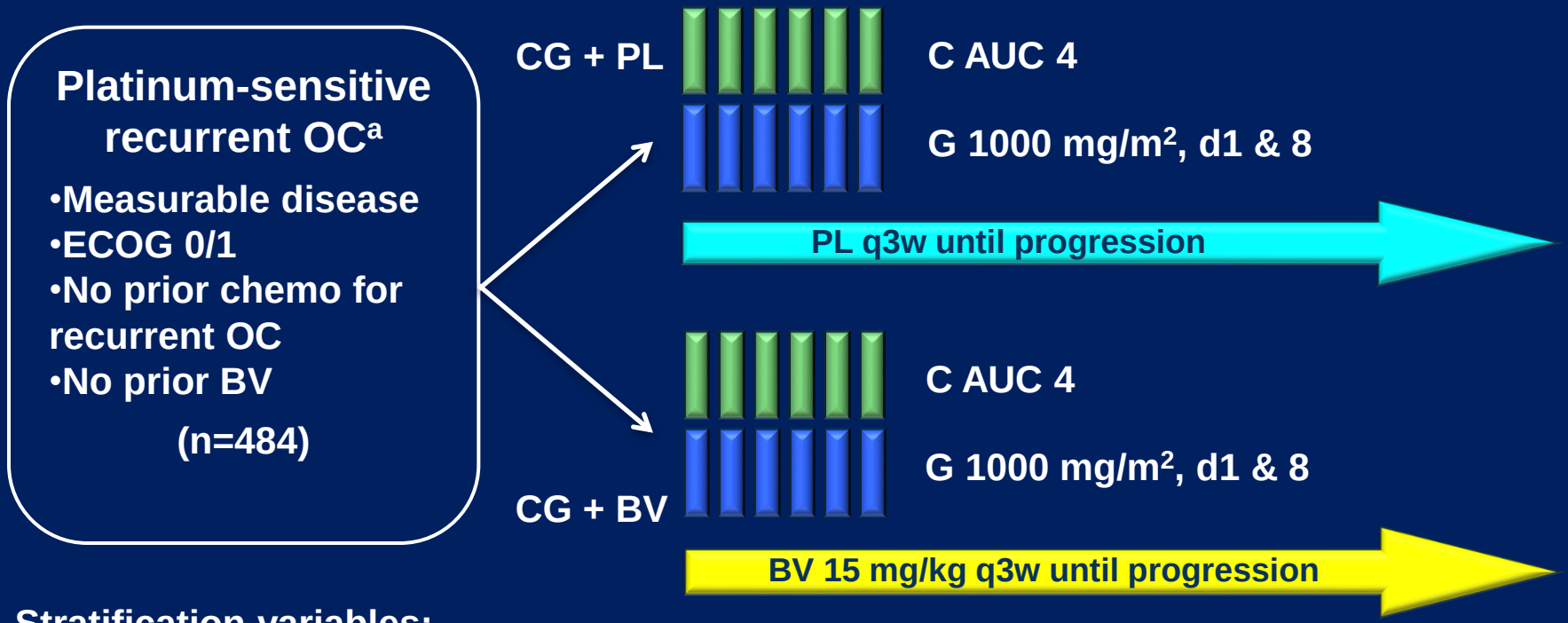
oCeans

Recurrent, platinum resistant

Recurrent, platinum sensitive

1. Avastin SmPC; 2. Perren, et al. NEJM 2011
3. Aghajanian, et al. JCO 2012; 4. Pujade-Lauraine, et al. ASCO 2012

OCEANS: Study schema



Stratification variables:

- Platinum-free interval (6–12 vs >12 months)
- Cytoreductive surgery for recurrent disease (yes vs no)

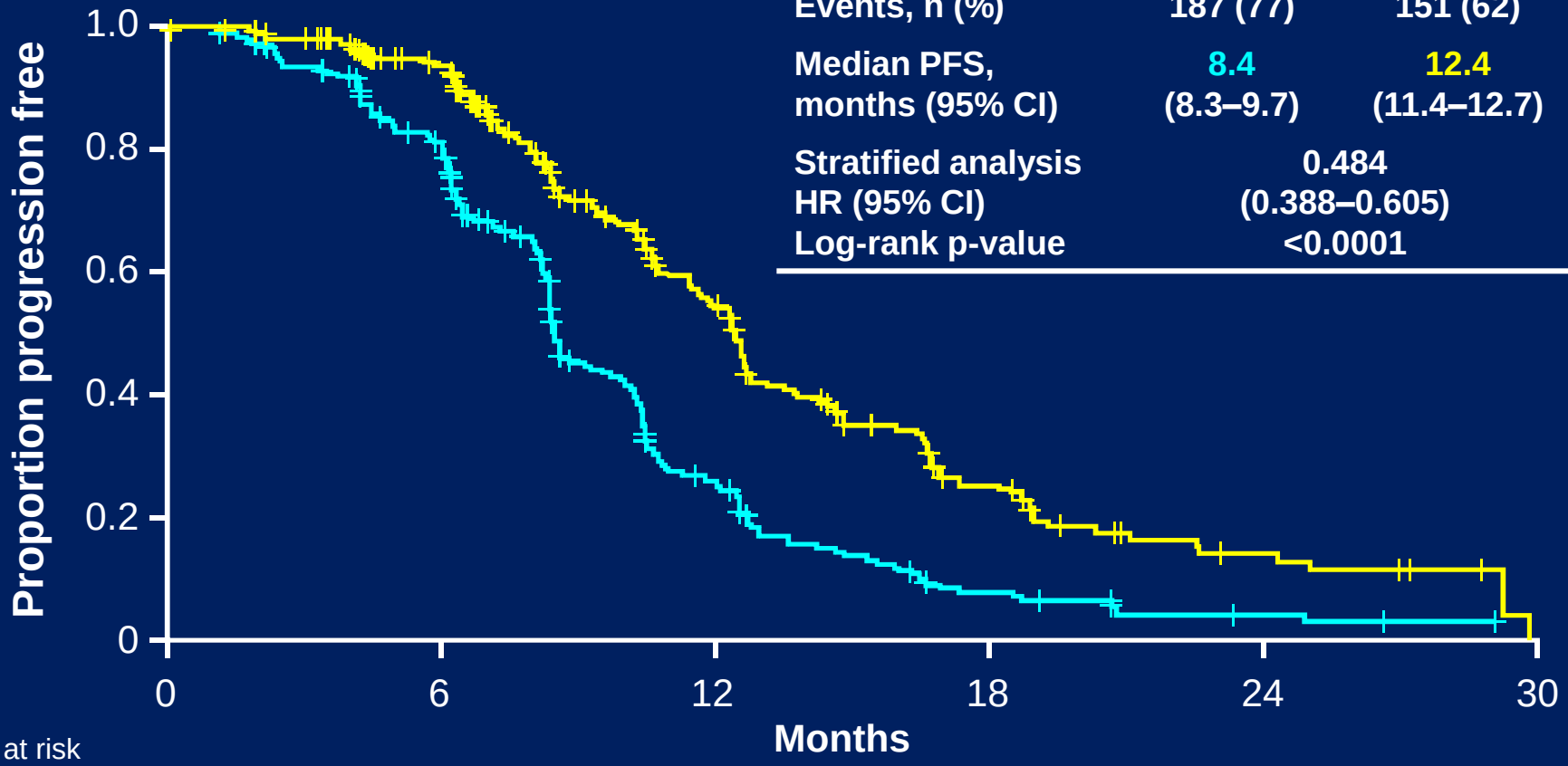
BV = bevacizumab; PL = placebo

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer

Aghajanian C, et al. J Clin Onco 2012

OCEANS: Primary analysis of PFS

	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI)	0.484 (0.388–0.605)	
Log-rank p-value	<0.0001	



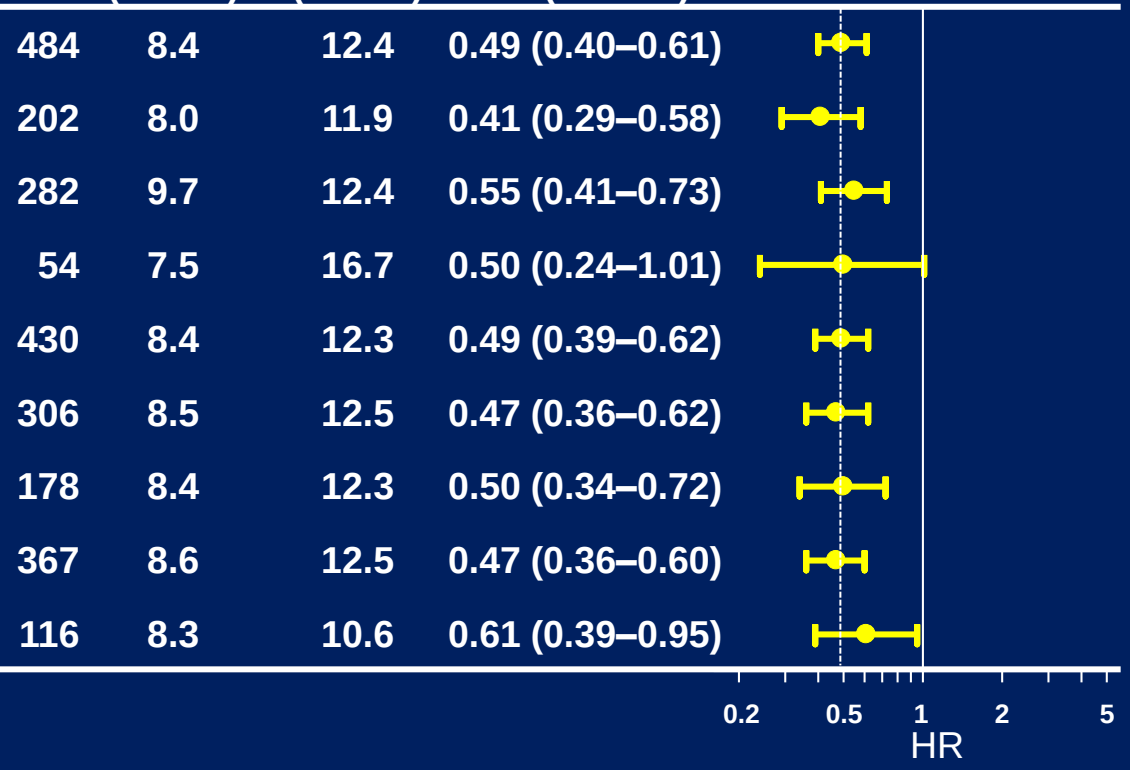
No. at risk

CG + PL	242	177	45	11	3	0
CG + BV	242	203	92	33	11	0

Aghajanian C, et al. J Clin Onco 2012

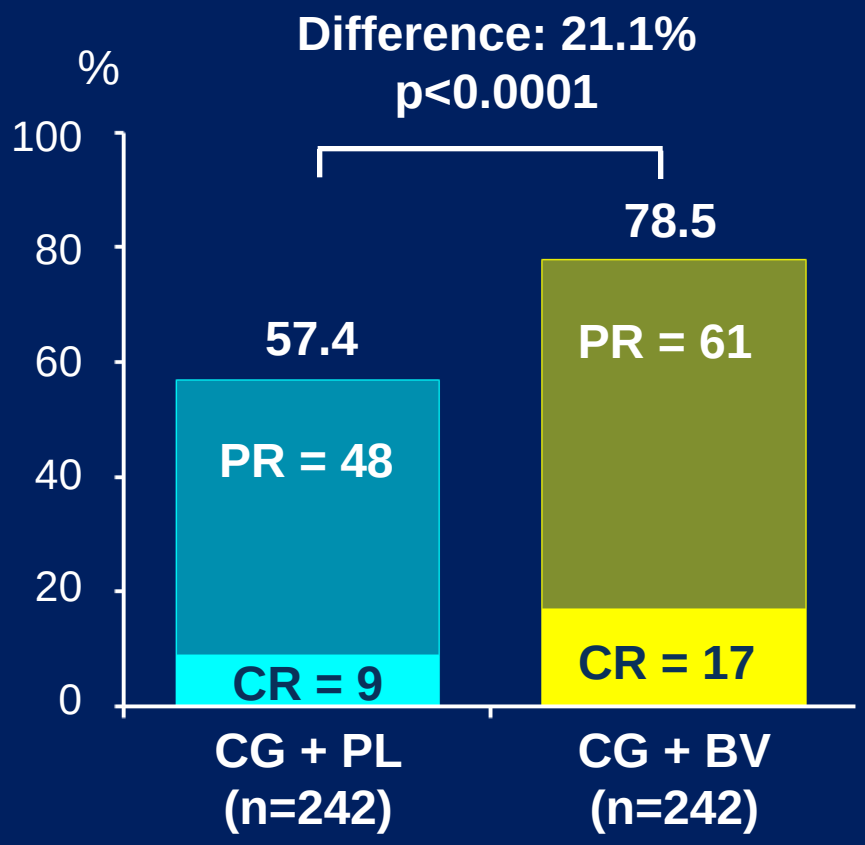
OCEANS: PFS subgroup analyses

Baseline risk factor		No. of patients	Median PFS (months) CG + PL (n=242)	Median PFS (months) CG + BV (n=242)	HR (95% CI)
All patients		484	8.4	12.4	0.49 (0.40–0.61)
Platinum-free interval, months	6–12	202	8.0	11.9	0.41 (0.29–0.58)
	>12	282	9.7	12.4	0.55 (0.41–0.73)
Cytoreductive surgery for recurrent disease	Yes	54	7.5	16.7	0.50 (0.24–1.01)
	No	430	8.4	12.3	0.49 (0.39–0.62)
Age, years	<65	306	8.5	12.5	0.47 (0.36–0.62)
	≥65	178	8.4	12.3	0.50 (0.34–0.72)
Baseline ECOG PS	0	367	8.6	12.5	0.47 (0.36–0.60)
	1	116	8.3	10.6	0.61 (0.39–0.95)



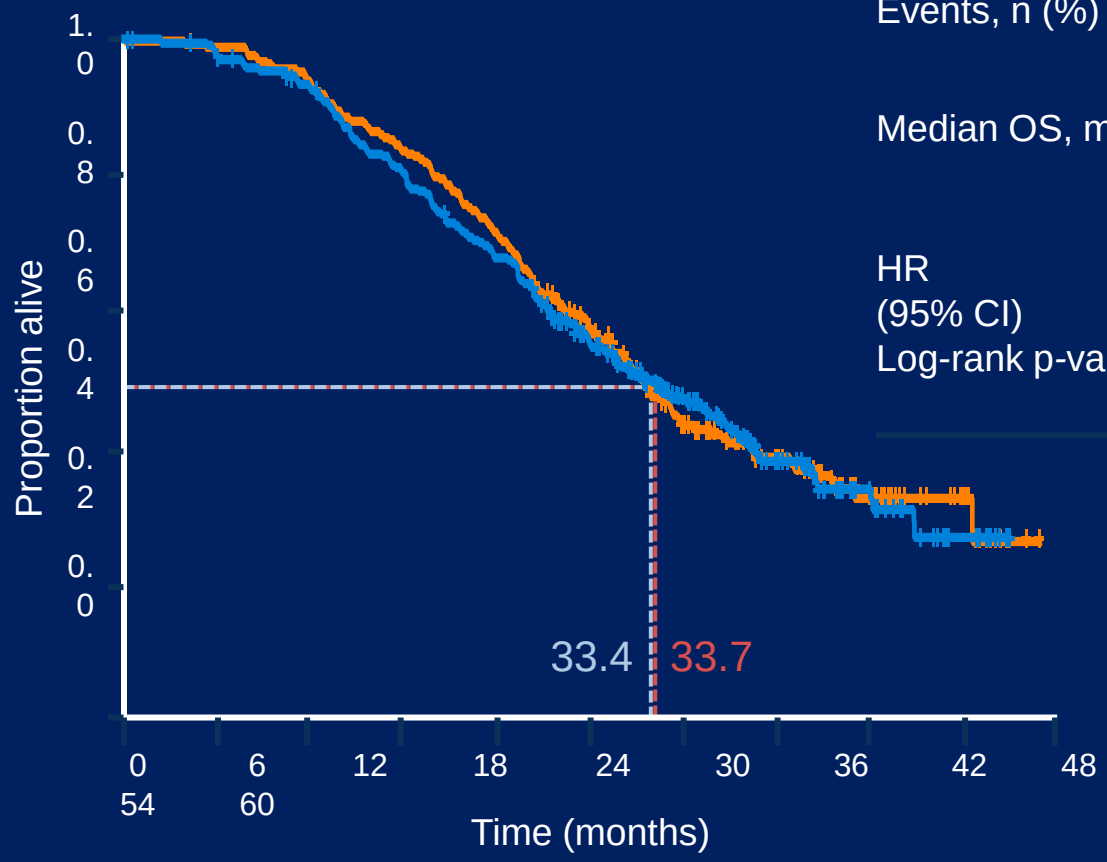
Aghajanian C, et al. J Clin Onco 2012

OCEANS: Objective response



Aghajanian C, et al. J Clin Onco 2012

OCEANS: Interim OS



	GC + PL (n=242)	GC + BV (n=242)
Events, n (%)	142 (58.7)	144 (59.5)
Median OS, months	**33.7**	**33.4**
HR (95% CI) Log-rank p-value	0.960 (0.760–1.214) p=0.7360	

Number at risk:

GC + PL	242	235	221	190	159	117	77	44	23	7	0
GC + BV	242	239	226	201	171	127	78	48	27	7	0

Aghajanian C, et al. J Clin Onco 2012

OCEANS: AEs of special interest

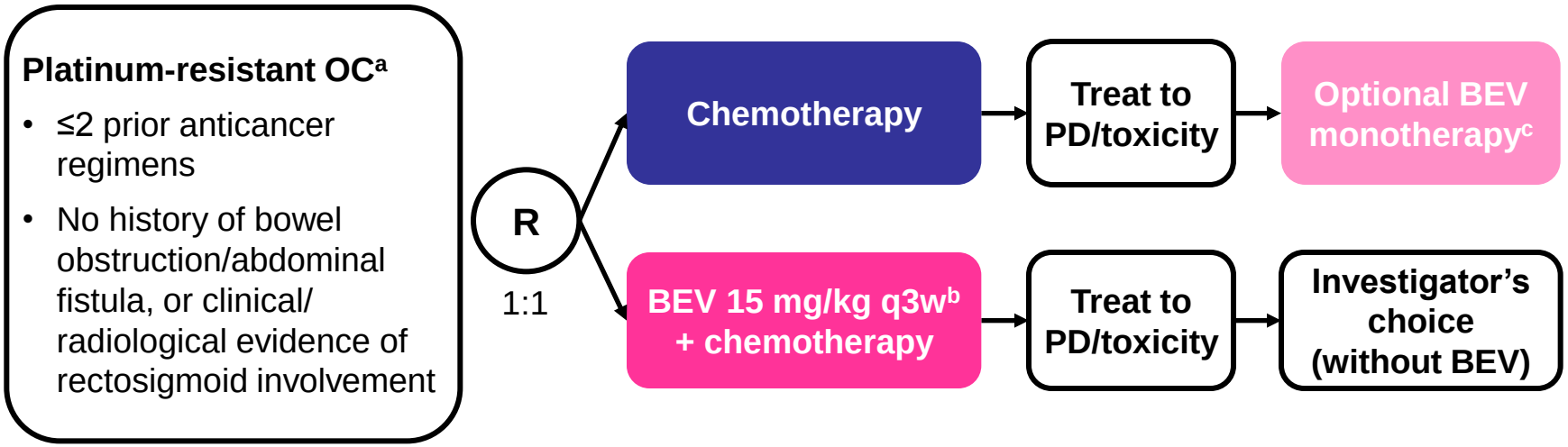
Patients, %	CG + PL (n=233)	CG + BV (n=247)
ATE, all grades	1	3
VTE, grade ≥3	3	4
CNS bleeding, all grades	<1	1
Non-CNS bleeding, grades ≥3	1	6
CHF, grades ≥3	1	1
Neutropenia, grade ≥3	56	58
Febrile neutropenia, grade ≥3	2	2
Hypertension, grade ≥3	<1	17
Fistula/abscess, all grades	<1	2
GI perforation, all grades	0	0[a]
Proteinuria, grade ≥3	1	9
RPLS, all grade	0	1
Wound-healing complication, grades ≥3	0	1

ATE = arterial thromboembolic event; CHF = congestive heart failure; GI = gastrointestinal; RPLS = reversible posterior leukoencephalopathy syndrome; VTE = venous thromboembolic event

[a]Two GI perforations occurred 69 days after last BV dose

Aghajanian C, et al. J Clin Onco 2012

AURELIA trial in resistant disease



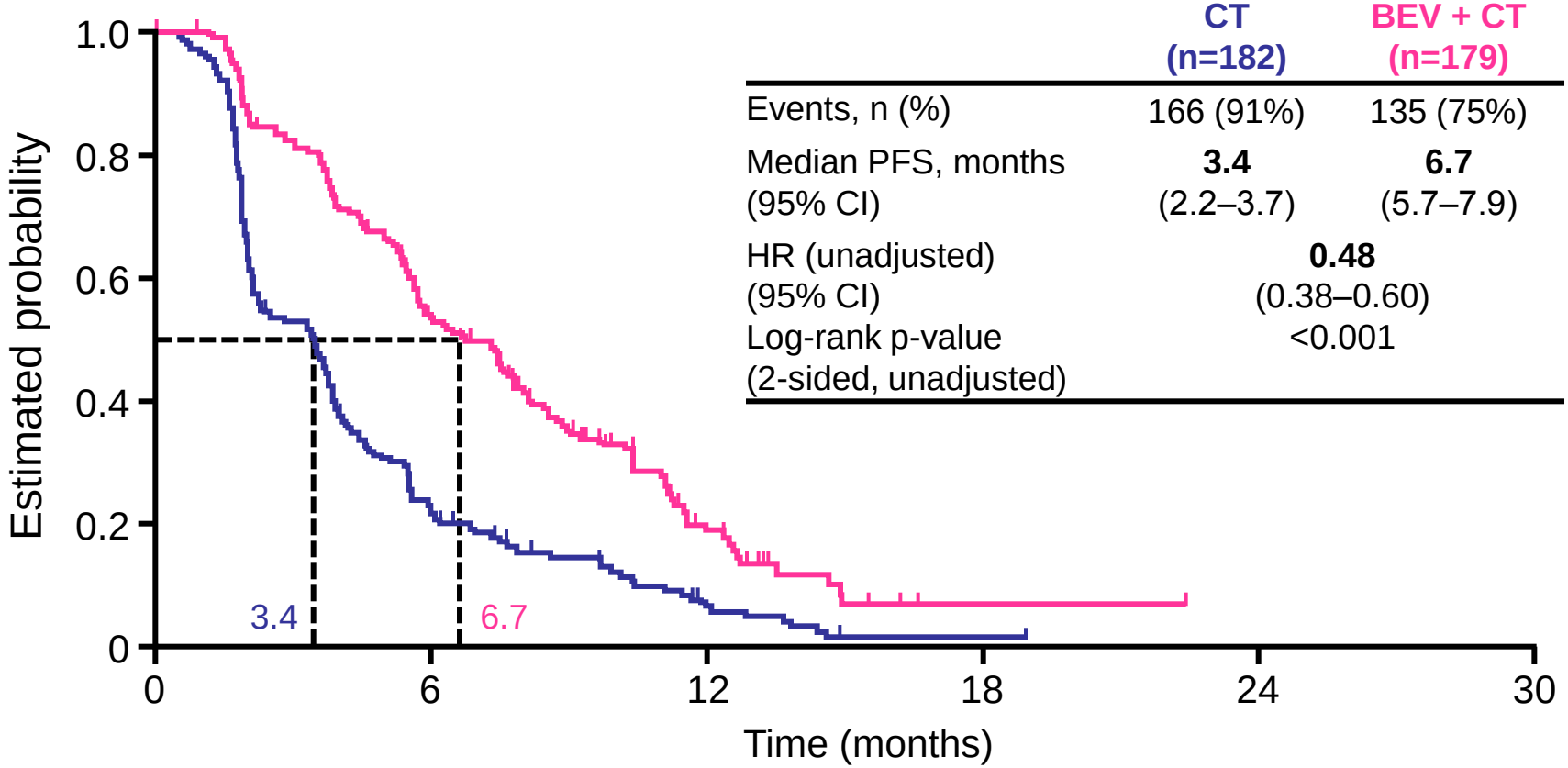
Chemotherapy options (investigator's choice):

- Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)
- PLD 40 mg/m^2 day 1 q4w

PD = progressive disease

Pujade-Lauraine E et al, ASCO 2012

Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

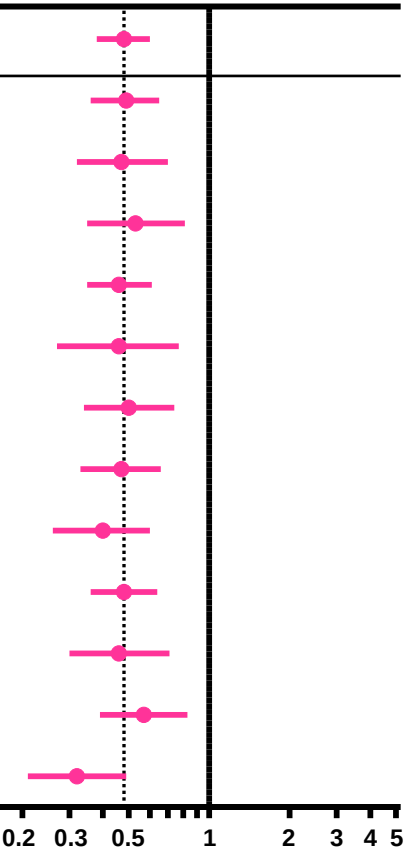
No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Pujade-Lauraine E et al, ASCO 2012

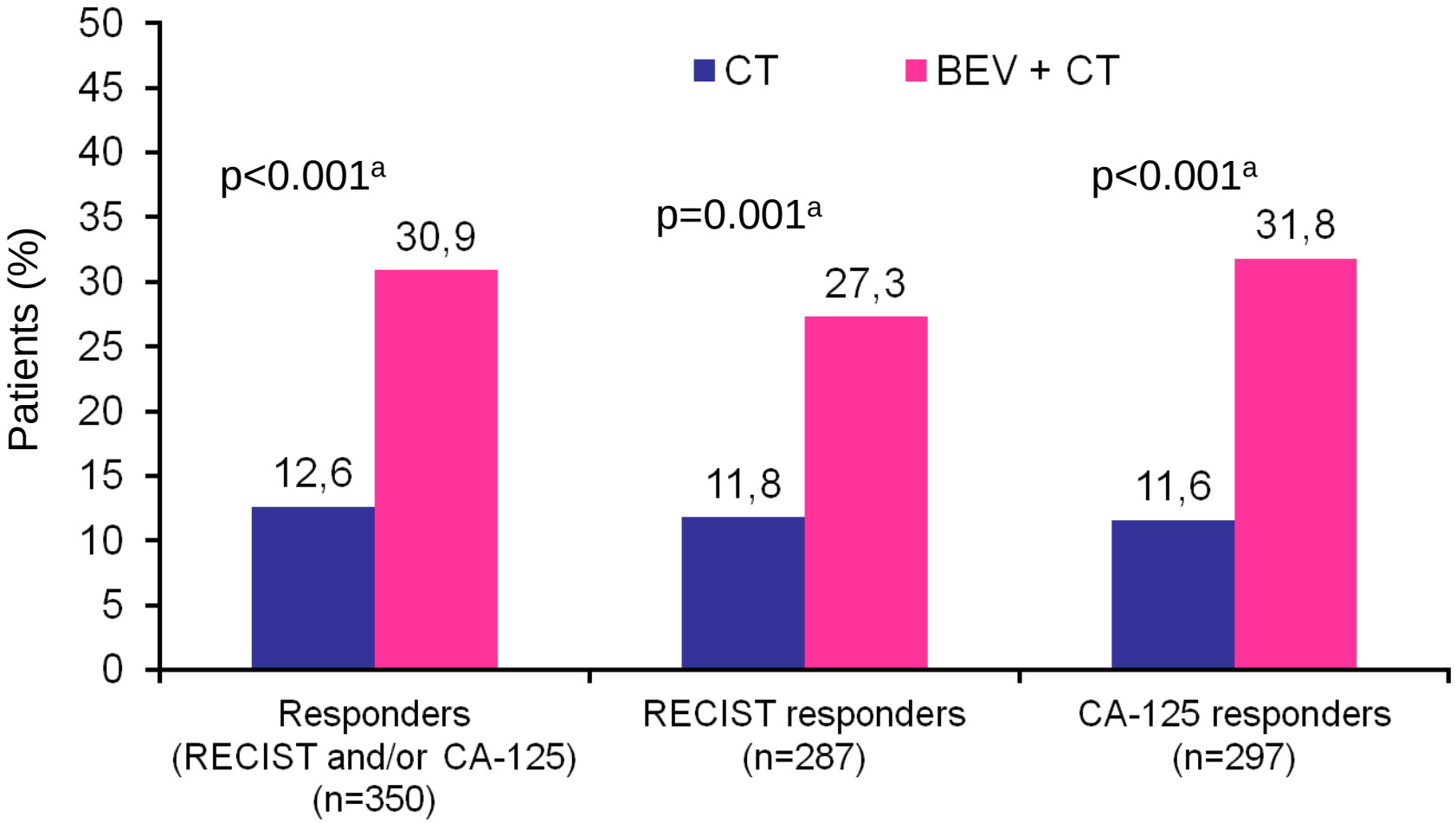
Subgroup analysis of PFS

Subgroup		No. of patients	Median PFS, months: CT	Median PFS, months: BEV + CT	HR[a]
All patients		361	**3.4**	**6.7**	0.48
Age, years	**<65**	228	**3.4**	**6.0**	0.49
	≥65	133	**3.5**	**7.8**	0.47
PFI, months[b]	**<3**	96	**2.1**	**5.4**	0.53
	3–6	257	**3.6**	**7.8**	0.46
Measurable disease, cm	**No (<1)**	74	**3.7**	**7.5**	0.46
	Yes (1–<5)	126	**3.3**	**7.5**	0.50
	Yes (≥5)	161	**3.3**	**6.0**	0.47
Ascites	**Yes**	113	**2.5**	**5.6**	0.40
	No	248	**3.5**	**7.6**	0.48
Chemotherapy	**Paclitaxel**	115	**3.9**	**10.4**	0.46
	PLD	126	**3.5**	**5.4**	0.57
	Topotecan	120	**2.1**	**5.8**	0.32



Pujade-Lauraine E et al, ASCO 2012

Summary of best overall response rates



[a]*Two-sided chi-square test with Schouten correction*

Adverse events of special interest

Grade ≥3 adverse events of special interest, n (%)	CT (n=181)	BEV + CT (n=179)
Hypertension	2 (1.1)	13 (7.3)
Grade ≥2	12 (6.6)	36 (20.1)
Proteinuria	0	3 (1.7)
Grade ≥2	1 (0.6)	19 (10.6)
GI perforation	0	3 (1.7)
Grade ≥2	0	4 (2.2)
Fistula/abscess	0	2 (1.1)
Grade ≥2	0	4 (2.2)
Bleeding	2 (1.1)	2 (1.1)
Thromboembolic event	8 (4.4)	9 (5.0)
Arterial	0	4 (2.2)
Venous	8 (4.4)	5 (2.8)
Wound-healing complication	0	0
RPLS	0	1 (0.6)
CHF	1 (0.6)	1 (0.6)
Cardiac disorders (excluding CHF)	0	0

RPLS = reversible posterior leukoencephalopathy syndrome; CHF = congestive heart failure

Conclusions

- AURELIA is the first randomized phase III trial in platinum-resistant OC to demonstrate:
  - Benefit with biologic therapy
  - Benefit with a combination regimen versus monotherapy

Bevacizumab combined with chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer

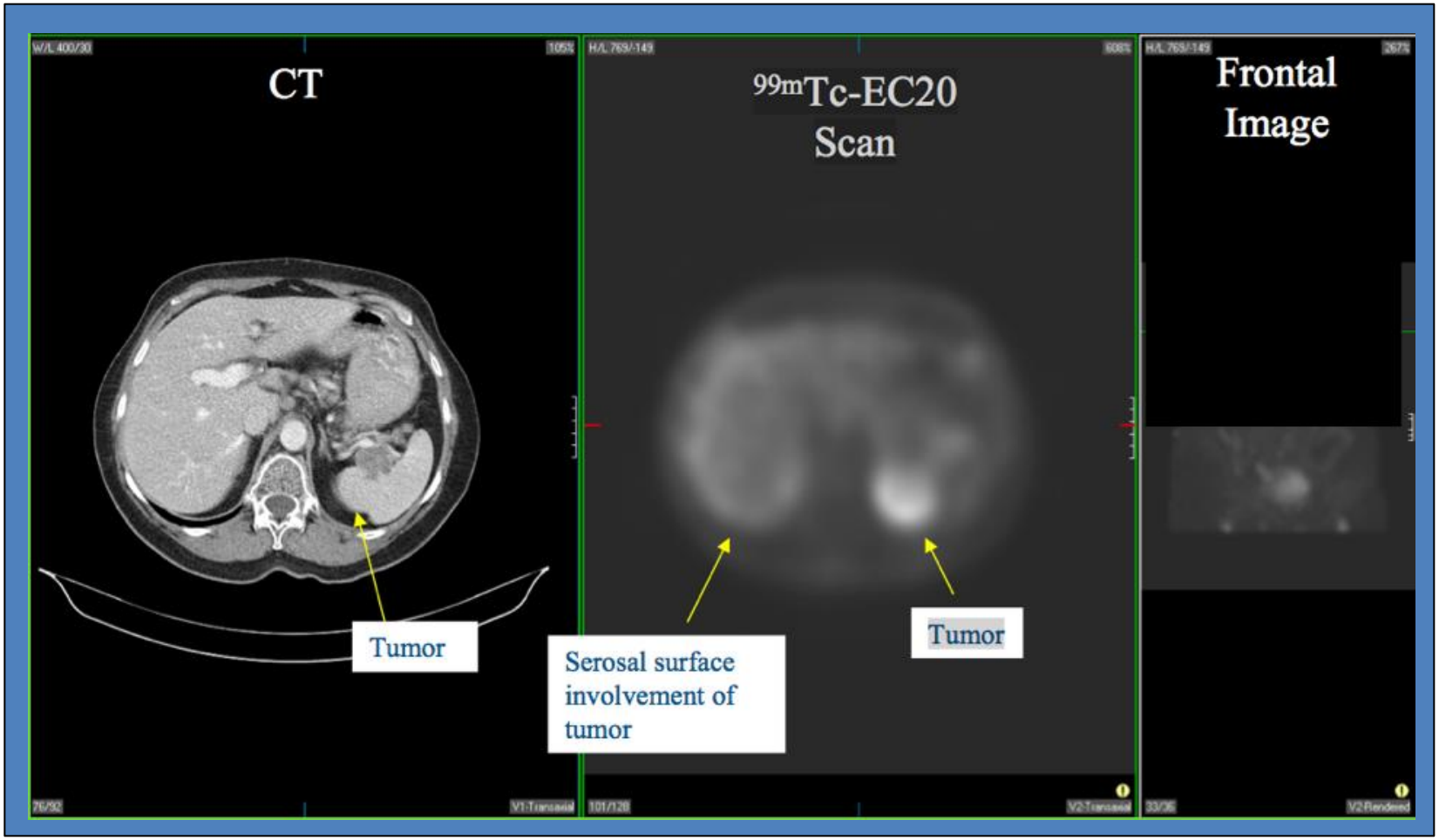
Pujade-Lauraine E et al, ASCO 2012

Significant ongoing interest in angiogenesis inhibition in ovarian cancer

Agent	Trial	Setting	Regimen	Estimated enrolment	Estimated primary completion date
Pazopanib	AGO-OVAR16 (NCT00866697)	Front-line	Pazopanib monotherapy versus placebo	**900**	March 2013
BIBF 1120	AGO-OVAR12 (NCT01015118)	Front-line	BIBF 1120 in combination with CP compared to placebo plus CP	**1300**	July 2016
AMG 386	TRINOVA-1 (NCT01204749)	Recurrent (partially platinum sensitive or platinum resistant)	AMG 386 or placebo, in combination with weekly paclitaxel	**900**	July 2013
	TRINOVA-2 (NCT01281254)		Pegylated liposomal doxorubicin (PLD) plus AMG 386 or placebo	**380**	April 2014
	TRINOVA-3 (NCT01493505)	Front-line	AMG 386 with CP followed by single-agent AMG 386	**2000**	May 2016
Bevacizumab	AGO-OVAR 17 (BOOST; NCT01462890)		Carboplatin/paclitaxel + bevacizumab (15 vs 30 months)	**800**	November 2018
	GOG-0262 (NCT01167712)	Front-line	CP (qw vs q3w) + bevacizumab	**625**	February 2012
	GOG-0252 (NCT00951496)		IV vs IP chemotherapy + bevacizumab	**1500**	January 2016
	GOG-0213 (NCT00565851)	Recurrent (platinum sensitive)	CP + bevacizumab	**660**	December 2009

Targeting folate receptor

Folate-receptor targeted imaging (EC20) identifies FR+ tumors prior to FR-targeted therapy



Farletuzumab phase II: results

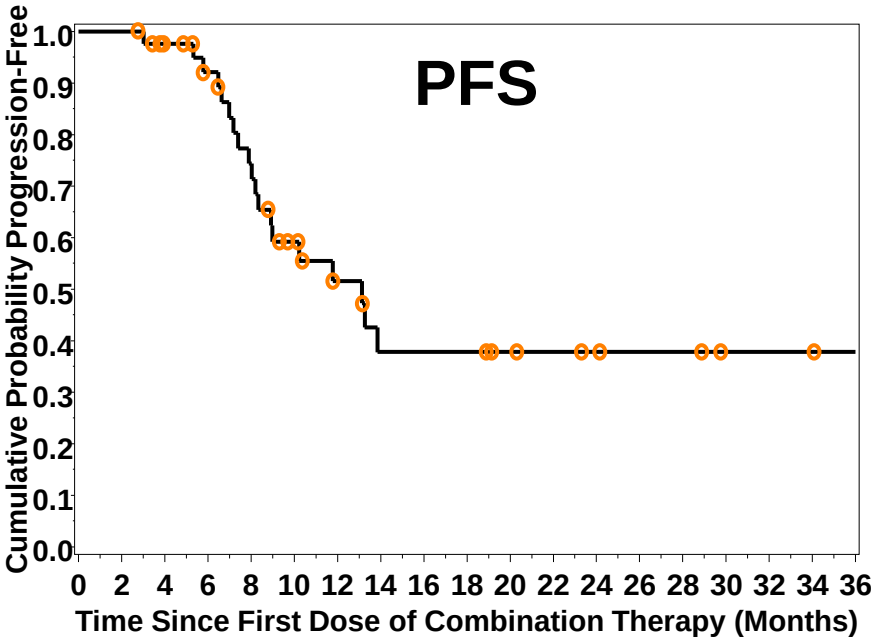
44 evaluable

5 did not normalize CA-125 (11.4%)

39 achieved normal CA-125 (88.6%)

3 achieved Rustin response (6.8%)

9 have second progression-free interval ≥ first (20.5%)

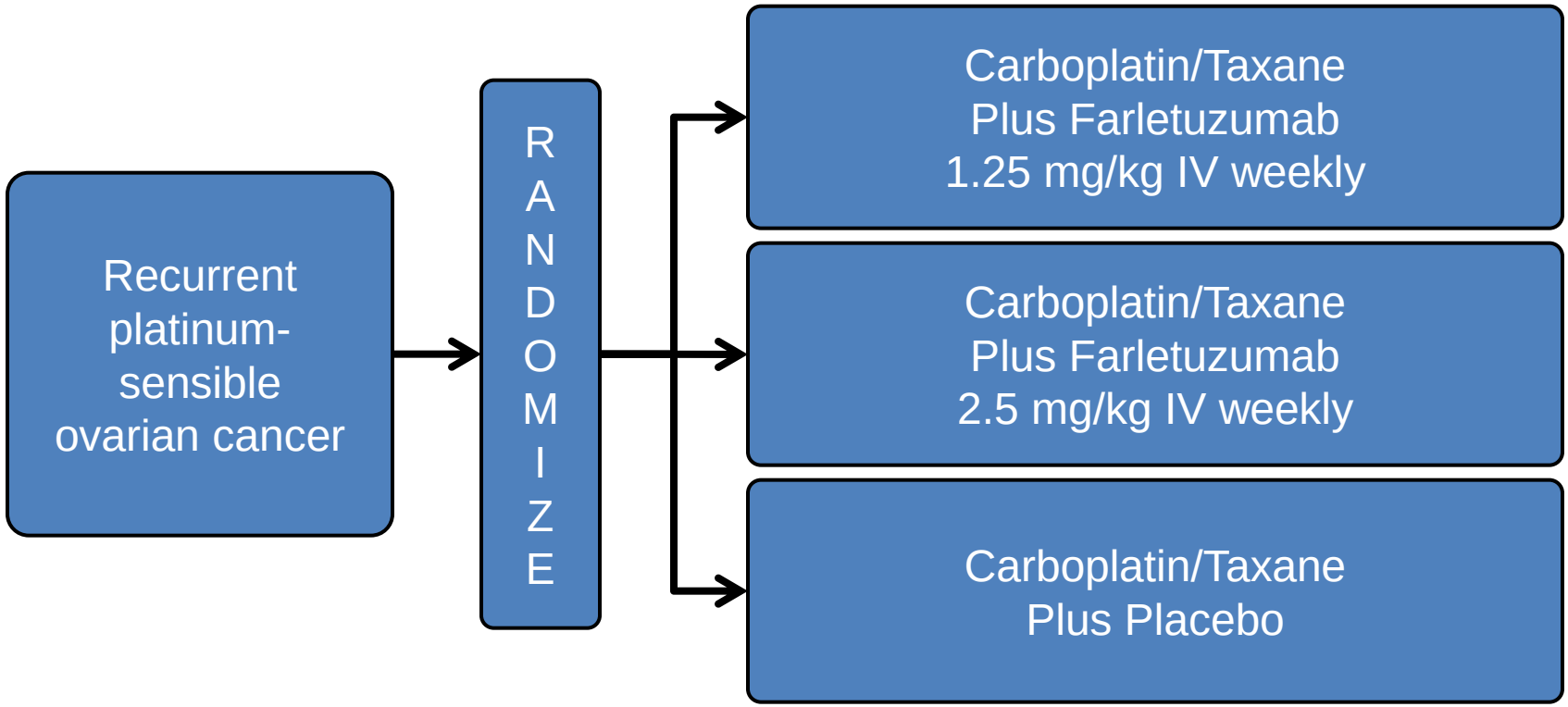


Armstrong D K, *et.al*.

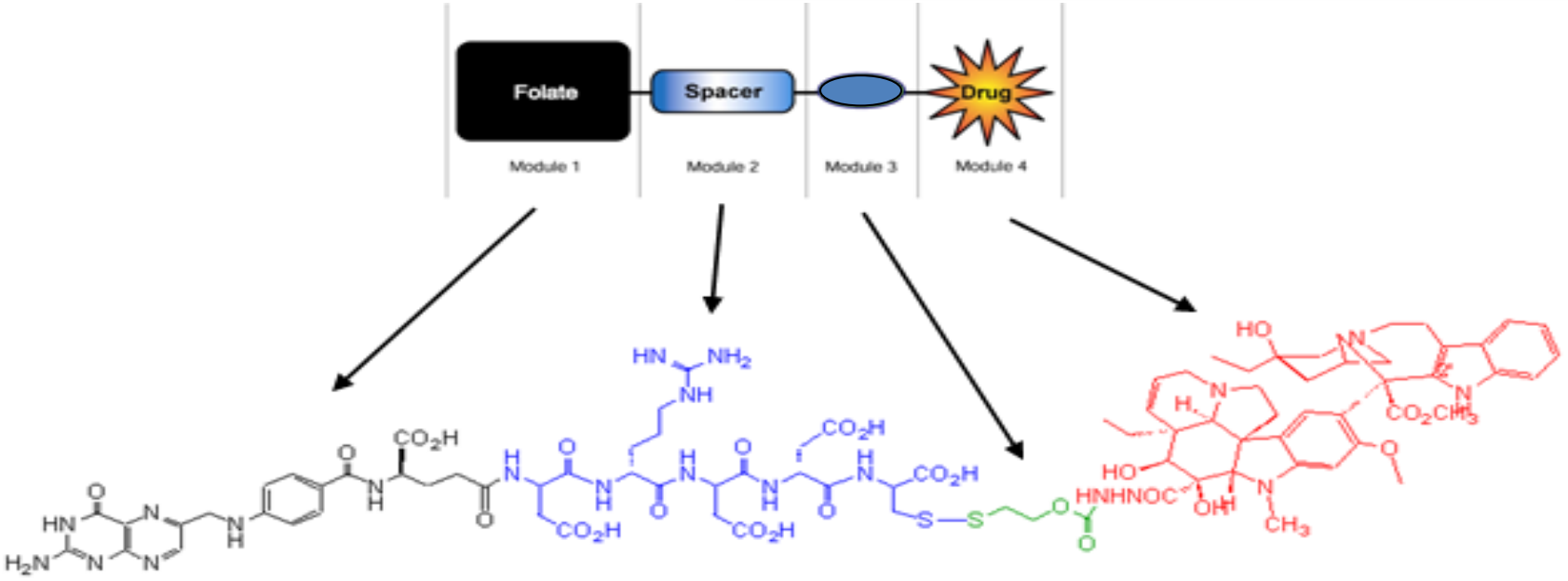
MORAb-003 (Farletuzumab) Randomized Phase III trial

Accrual ongoing (target accrual: 900 patients)
1:1:1 randomization

Primary endpoint: PFS

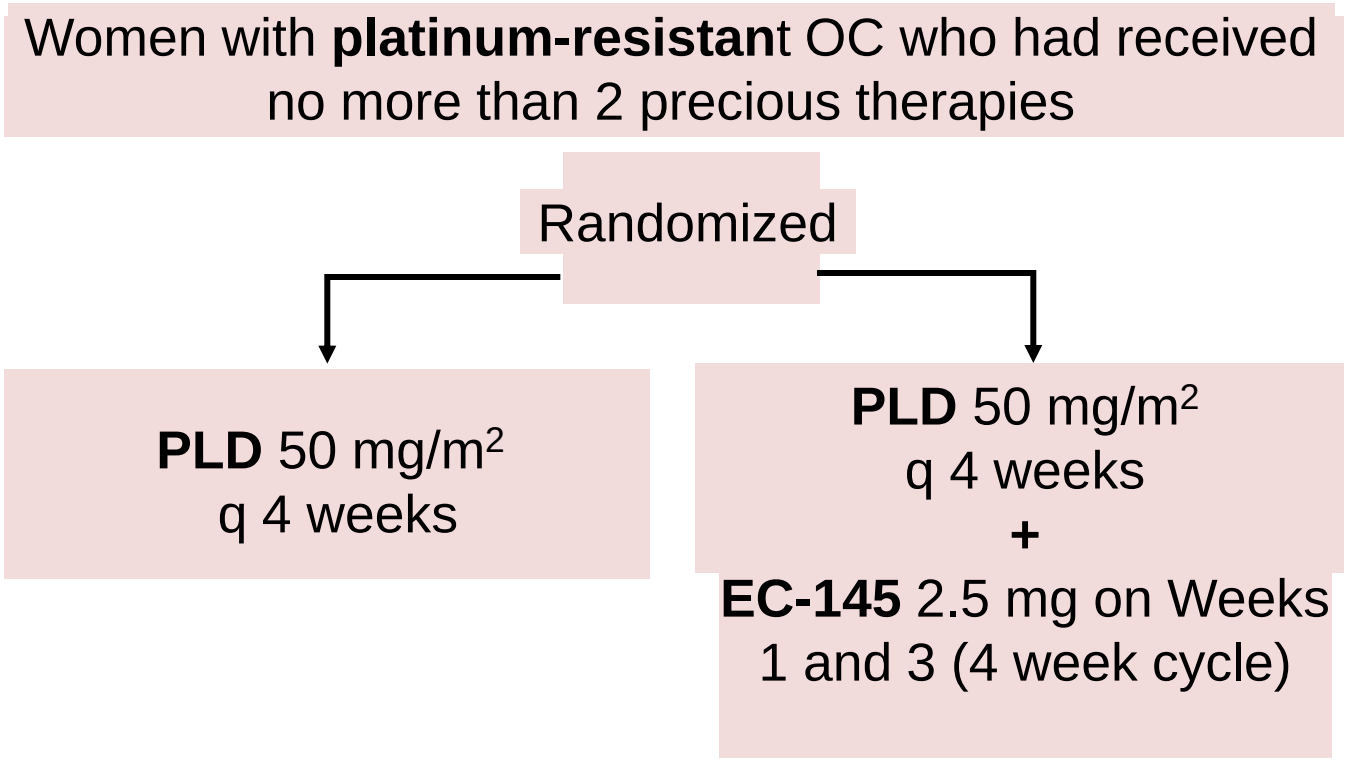


EC145



- EC145 is a conjugate of folate and the vinca alkaloid desacetylvinblastine hydrazide (DAVLBH)
- EC145 binds to the folate receptor FR and delivers DAVLBH into the cell via endocytosis

EC-FV-04 (PRECEDENT) Study Design



Naumann RW, et al. ASCO 2010

EC-FV-04 (PRECEDENT) Results

Response rate

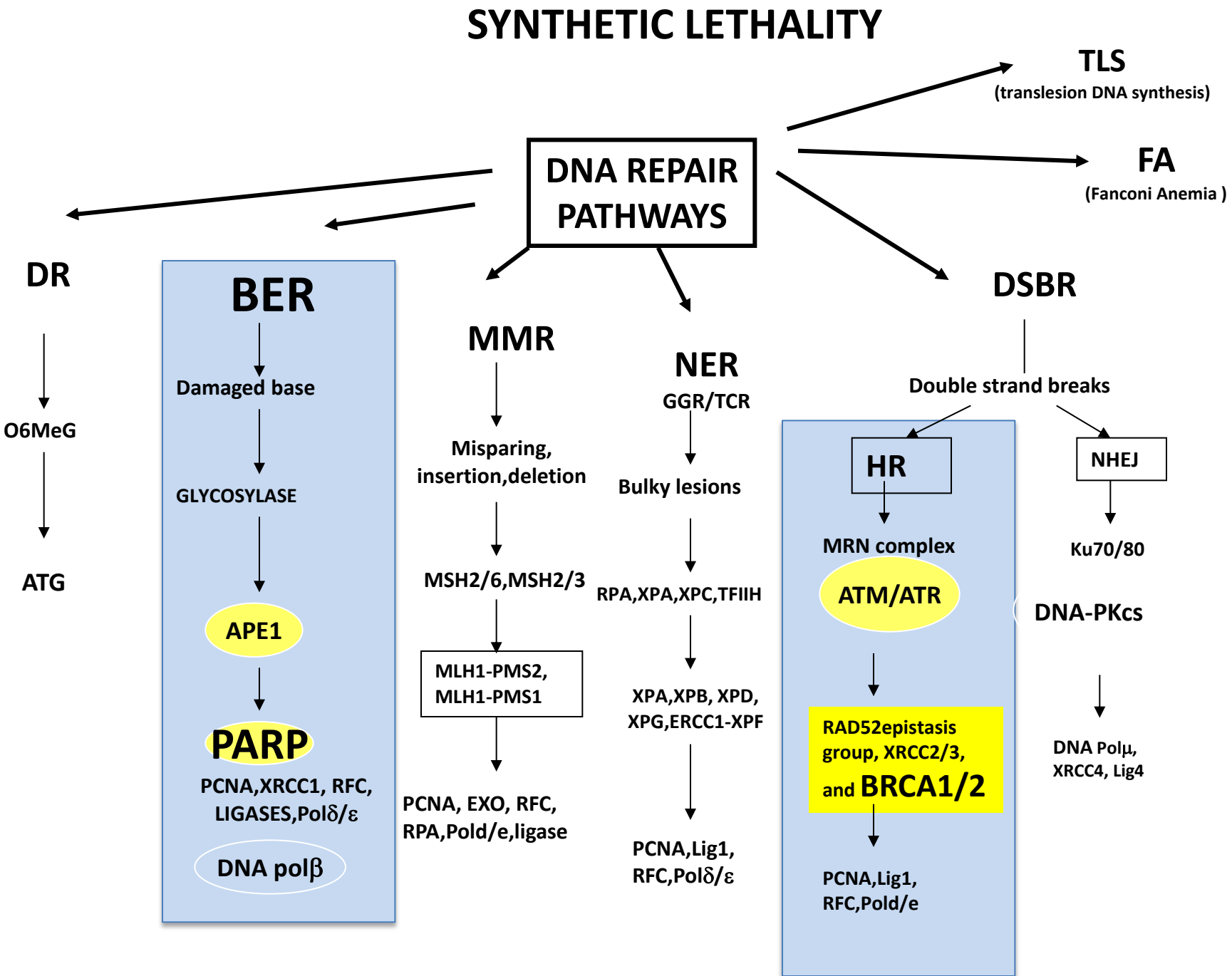
	EC145/PLD (n=54)	PLD (n=27)
Complete Response (CR)[2]	0 (0%)	0 (0.0%)
Partial Response (PR)[2]	**9 (16.7%)**	**4 (14.8%)**
Stable Disease (SD)[2]	**33 (61.1%)**	**12 (44.4%)**

PFS

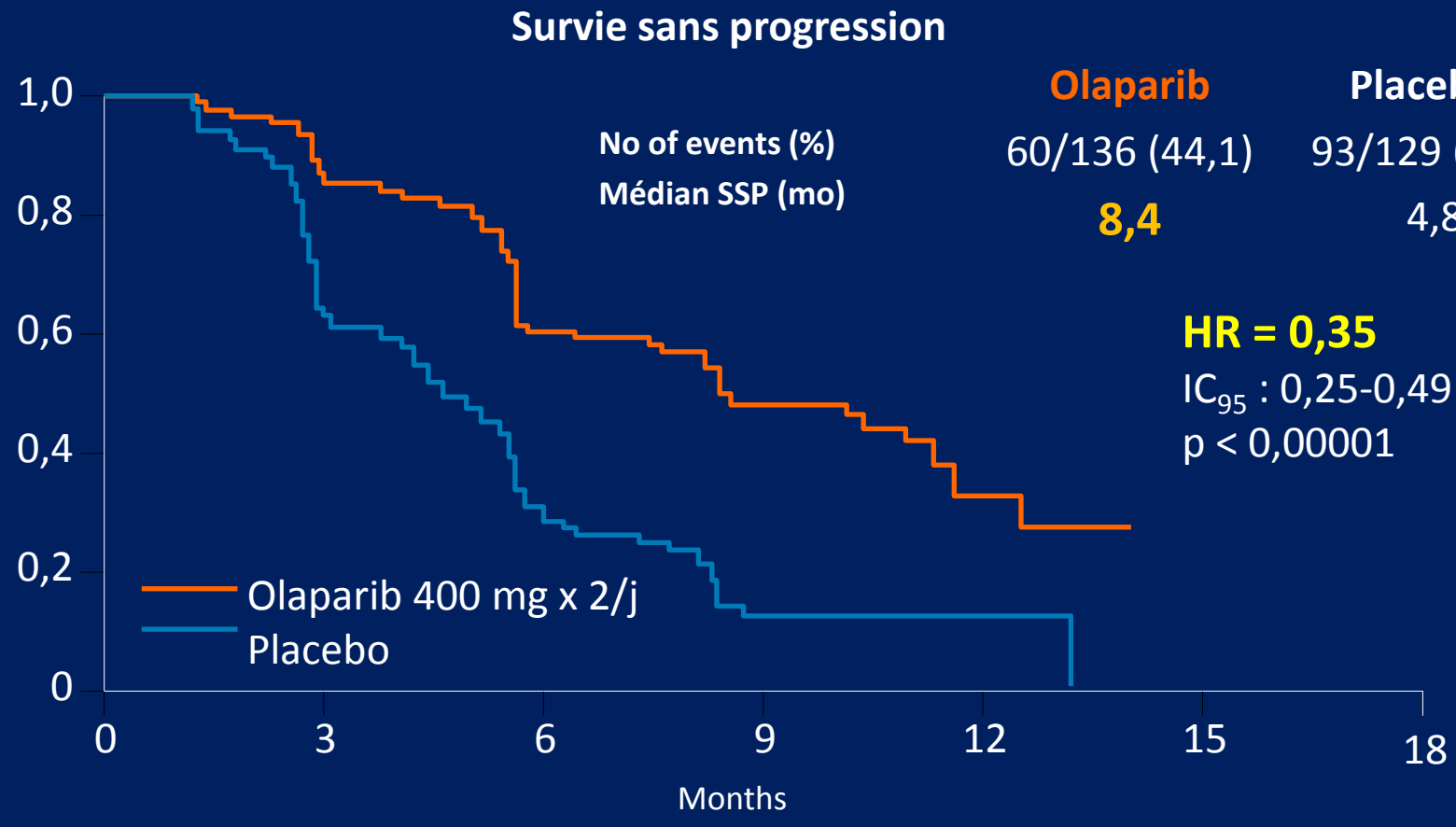
Findings	EC145 + PLD (n=60)	PLD (n=31)	P-value	Hazard Ratio
PFS	**24.0 weeks**	**11.7 weeks**	**0.014**	**0.497**

Naumann RW, et al. ASCO 2010

Inhibition de PARP
poly (ADP-ribose) polymerase


SYNTHETIC LETHALITY
TLS
(translesion DNA synthesis)
FA
(Fanconi Anemia)
DNA REPAIR PATHWAYS
DR
O6MeG
ATG
BER
Damaged base
GLYCOSYLASE
APE1
PARP
PCNA,XRCC1, RFC, LIGASES,Polδ/ε
DNA polβ
MMR
Misparing, insertion,deletion
MSH2/6,MSH2/3
MLH1-PMS2, MLH1-PMS1
PCNA, EXO, RFC, RPA,Pold/e,ligase
NER
GGR/TCR
Bulky lesions
RPA,XPA,XPC,TFIIH
XPA,XPB, XPD, XPG,ERCC1-XPF
PCNA,Lig1, RFC,Polδ/ε
DSBR
Double strand breaks
HR
MRN complex
ATM/ATR
RAD52epistasis group, XRCC2/3, and BRCA1/2
PCNA,Lig1, RFC,Pold/e
NHEJ
Ku70/80
DNA-PKcs
DNA Polμ, XRCC4, Lig4

Olaparib in maintenance of platinum-sensitive high grade serous ovarian cancer

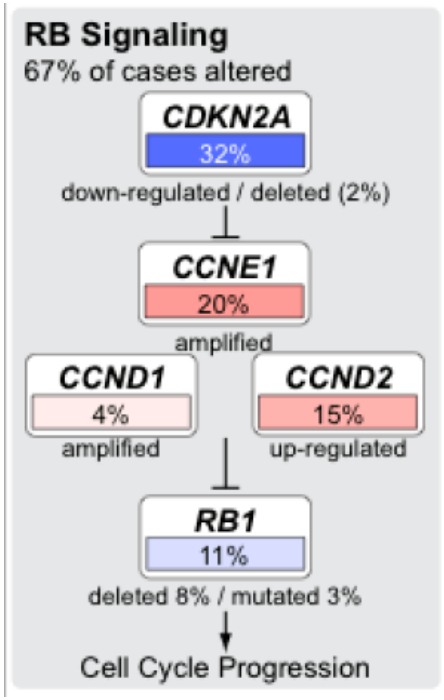


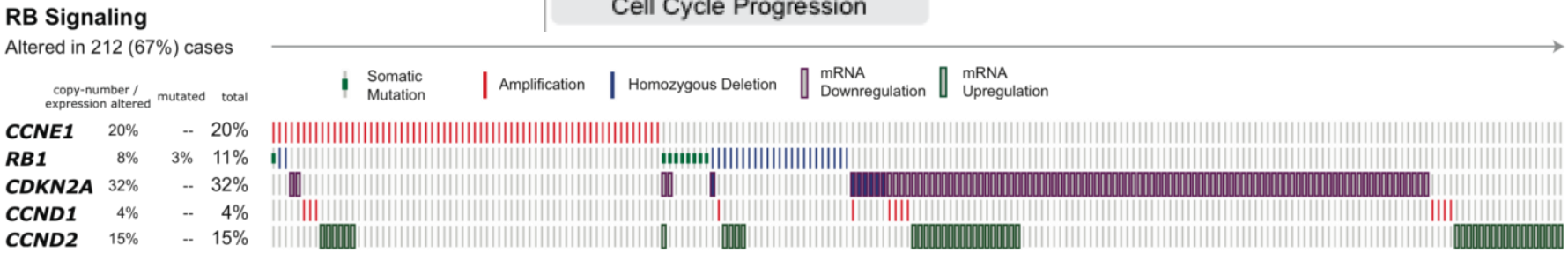
Olaparib	136	104	51	23	6	0	0
Placebo	129	72	23	7	1	0	0

D'après Ledermann JA et al., abstr. 5003 actualisé

Preferential pathway alterations

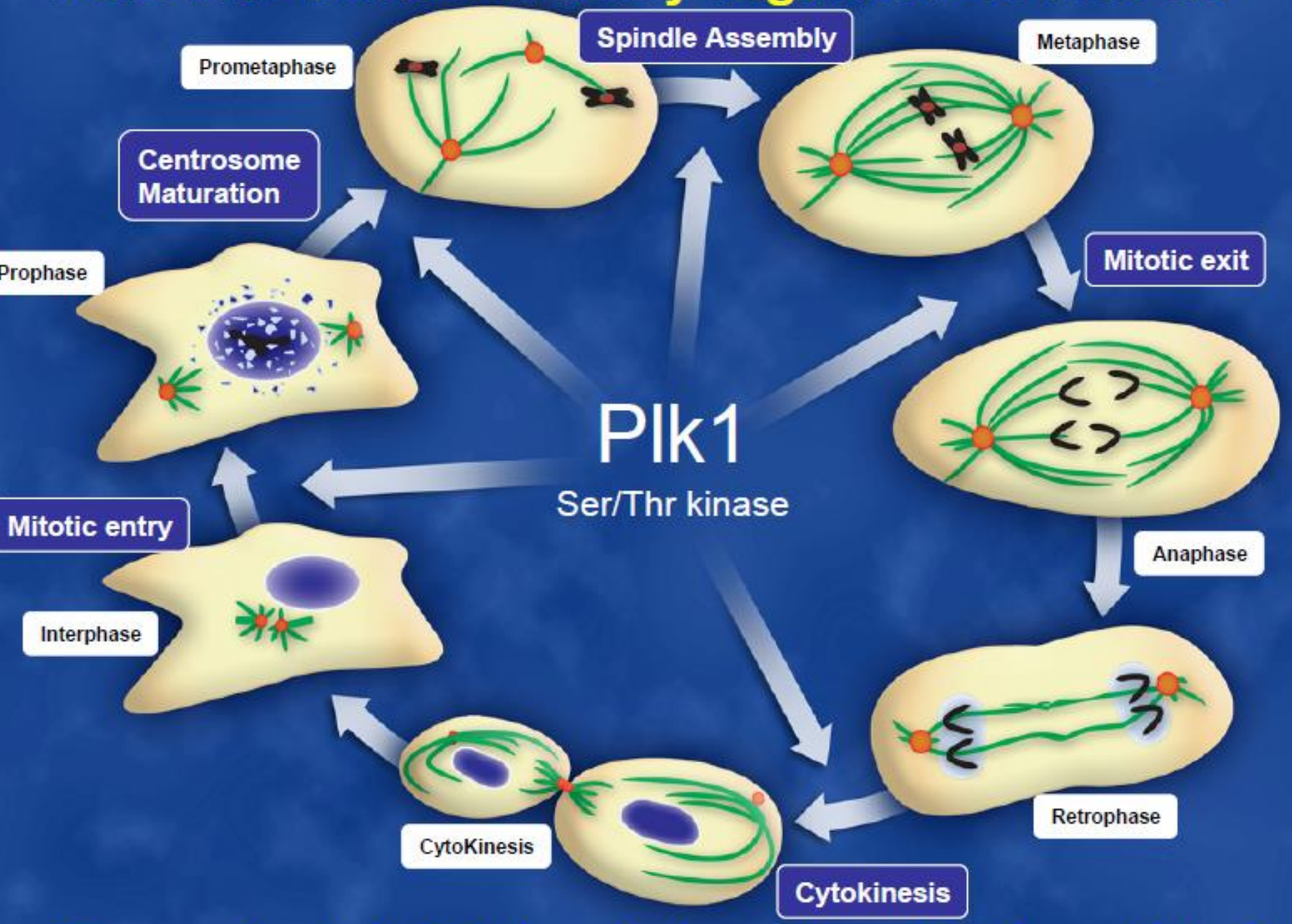
Retinoblastoma signaling and Cell Cycle progression





Cancer Genome Atlas Research Network.Nature, 2011

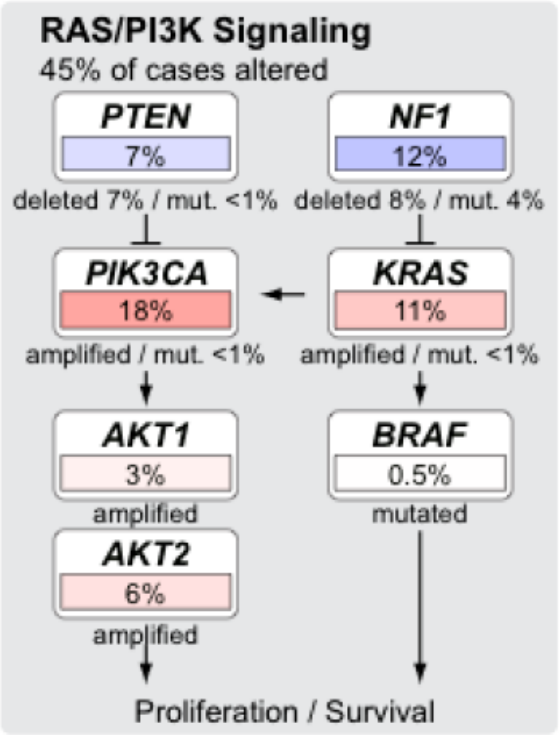
Polo-like kinase 1: a key regulator of mitosis



- ***Expressed exclusively during mitosis – no known function outside mitosis***

Preferential pathway alterations

RAS/PIK3 signaling

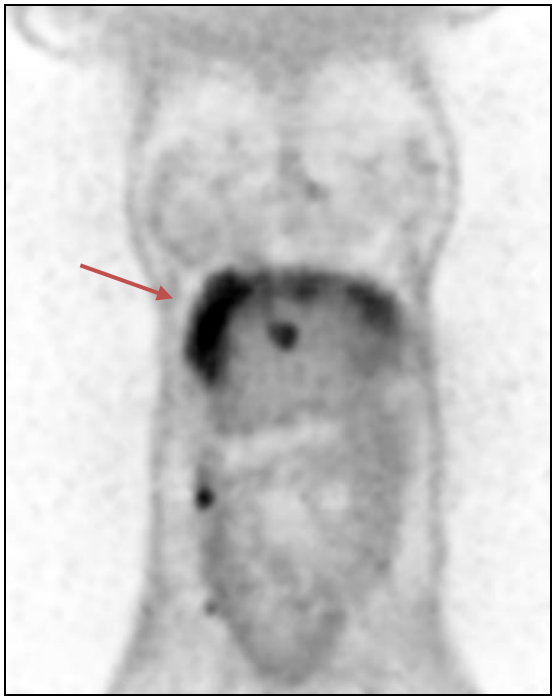


Cancer Genome Atlas Research Network.Nature, 2011

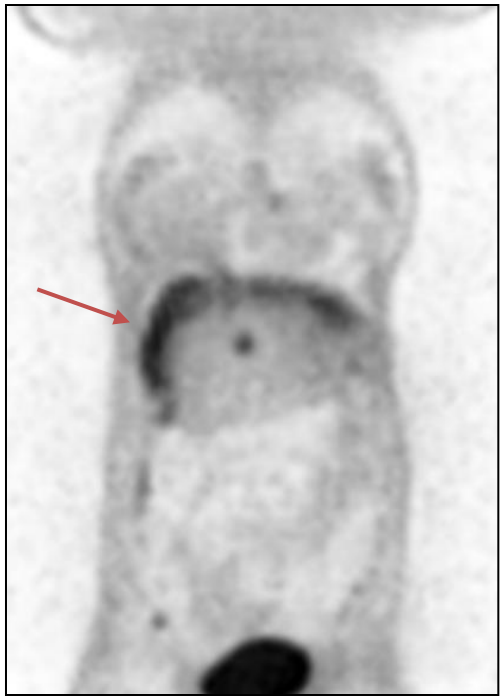
PHASE I TRIAL OF AN ORAL PI3K KINASE INHIBITOR: CLINICAL ACTIVITY IN OVARIAN CANCER

- 49 y/o female with ovarian cancer; liver & peritoneal disease
  - PTEN negative by IHC
  - 5 prior chemotherapies; Dx 2004
  - 100 mg QD GDC-0941 with AUC ~6.7 µM•hr
  - Best Response-SD, continues on-study >61 days
  - FDG-PET: 30% decrease in mean SUV_{max} end of C2

36% decrease SUVmax in perihepatic disease

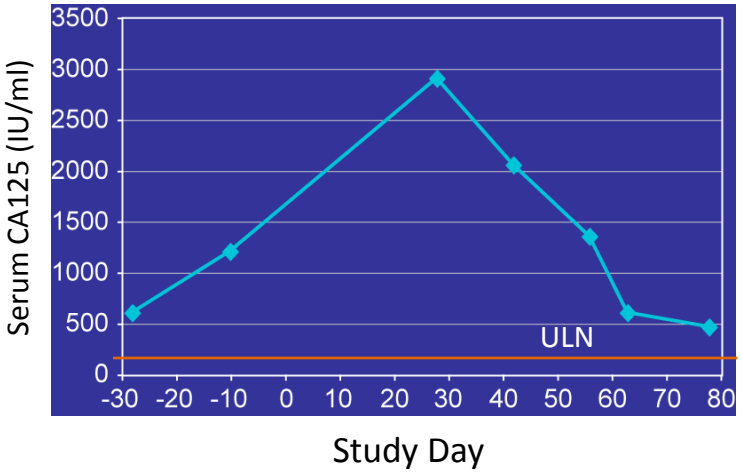


Baseline: SUVmax = 10.7



End C2: SUVmax = 6.8

CA125 response observed



S Kayes et al

Conclusions

- **Categorization of recurrent patients according to their platinum-free interval has allowed to better adapt chemotherapy regimens**
- **Inhibition of vascularization has shown its efficacy**
- **The central pathways of p53 (anti-PARP), Rb, and PI3K are all targets of high opportunity**