Trabectedine & Cancer de l'ovaire
Révisons nos standards

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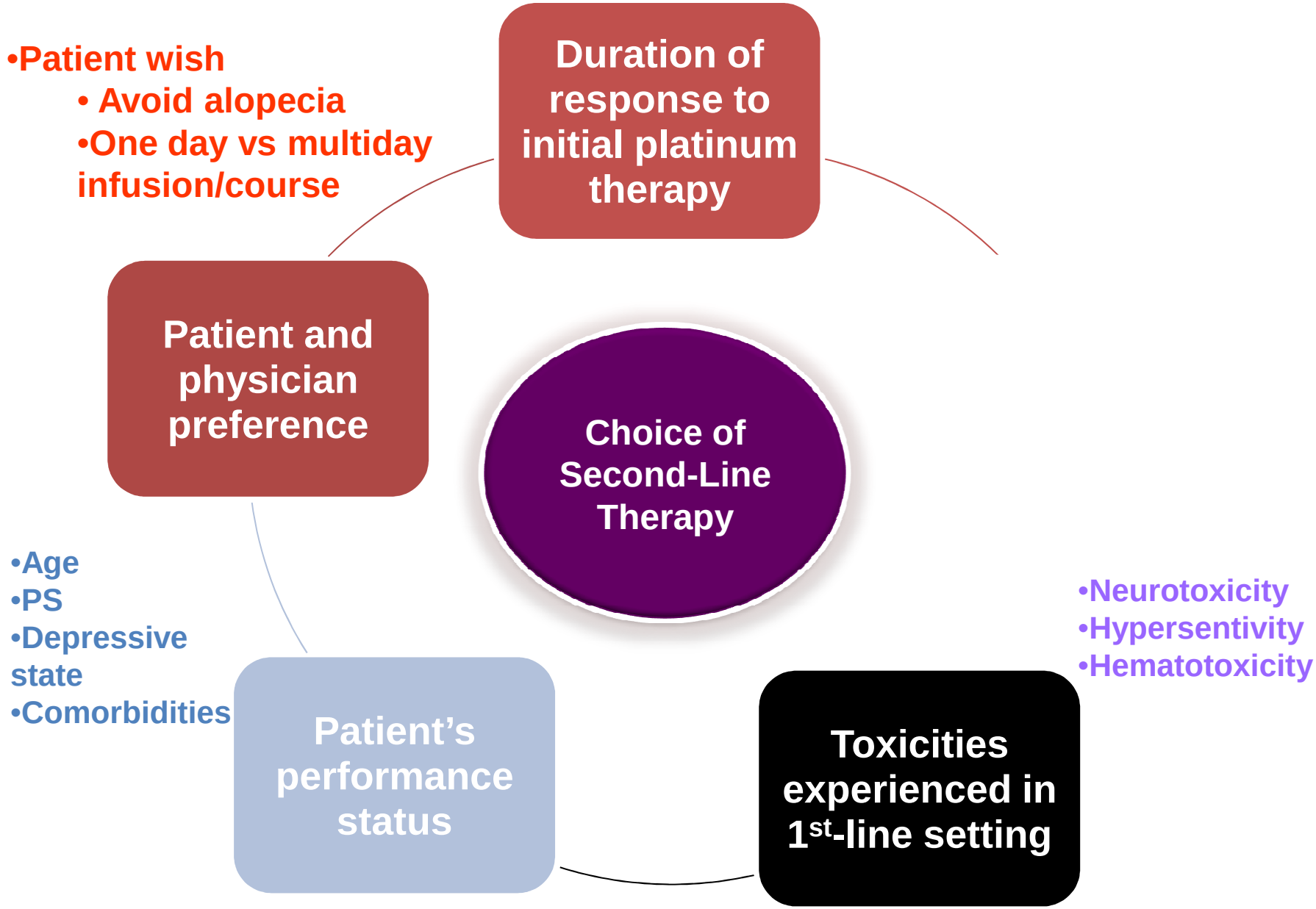
CANCER OVAIRE EN RECHUTE

Key Issues

- **Quand traiter?**
- **Que/quoi traiter ?**
- **Comment traiter ?**
  - **Chirurgie?**
  - **Single-agent vs combination / platinum vs non-platinum?**
  - **Quand s'arrêter?**
- **Questions qui dépendent des buts & des souhaits**

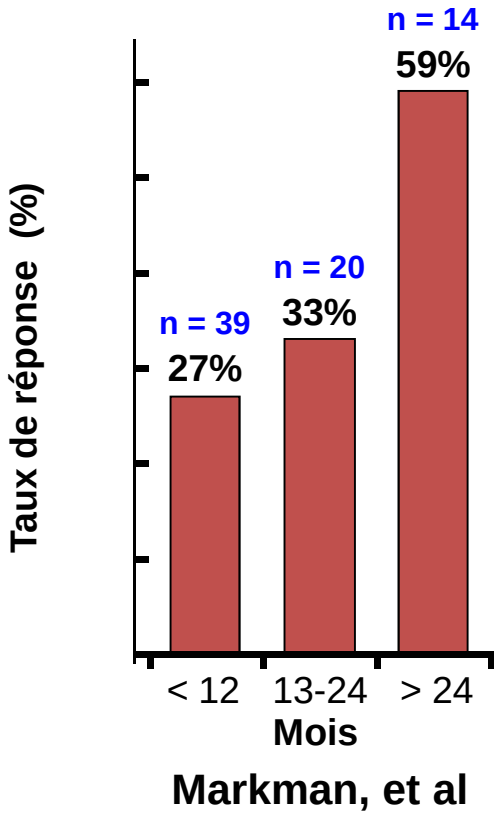
The Ideal Goal

Maximum time without symptoms and without treatment toxicity

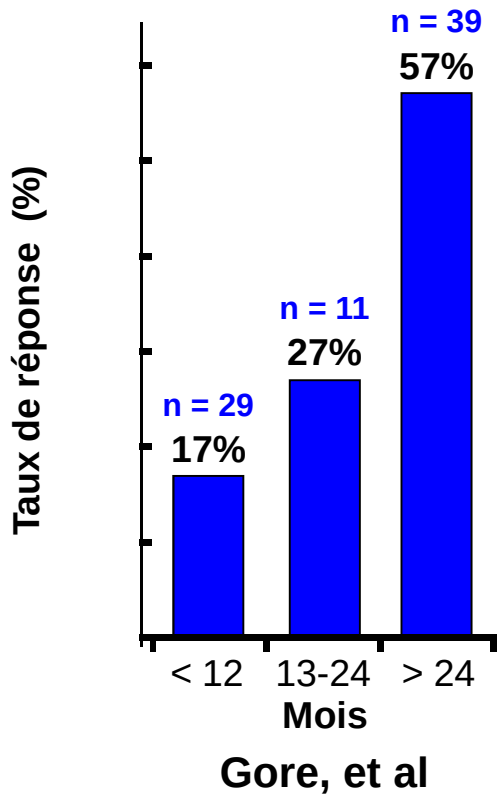


Armstrong. The Oncologist. 2002;7(suppl 5):20-28; Markman and Bookman. The Oncologist. 2000;5:26-35; Salzberg et al. Oncology. 2005;68:293-298.

Taux de réponse en fonction de l'intervalle libre sans sel de platine



Markman, et al

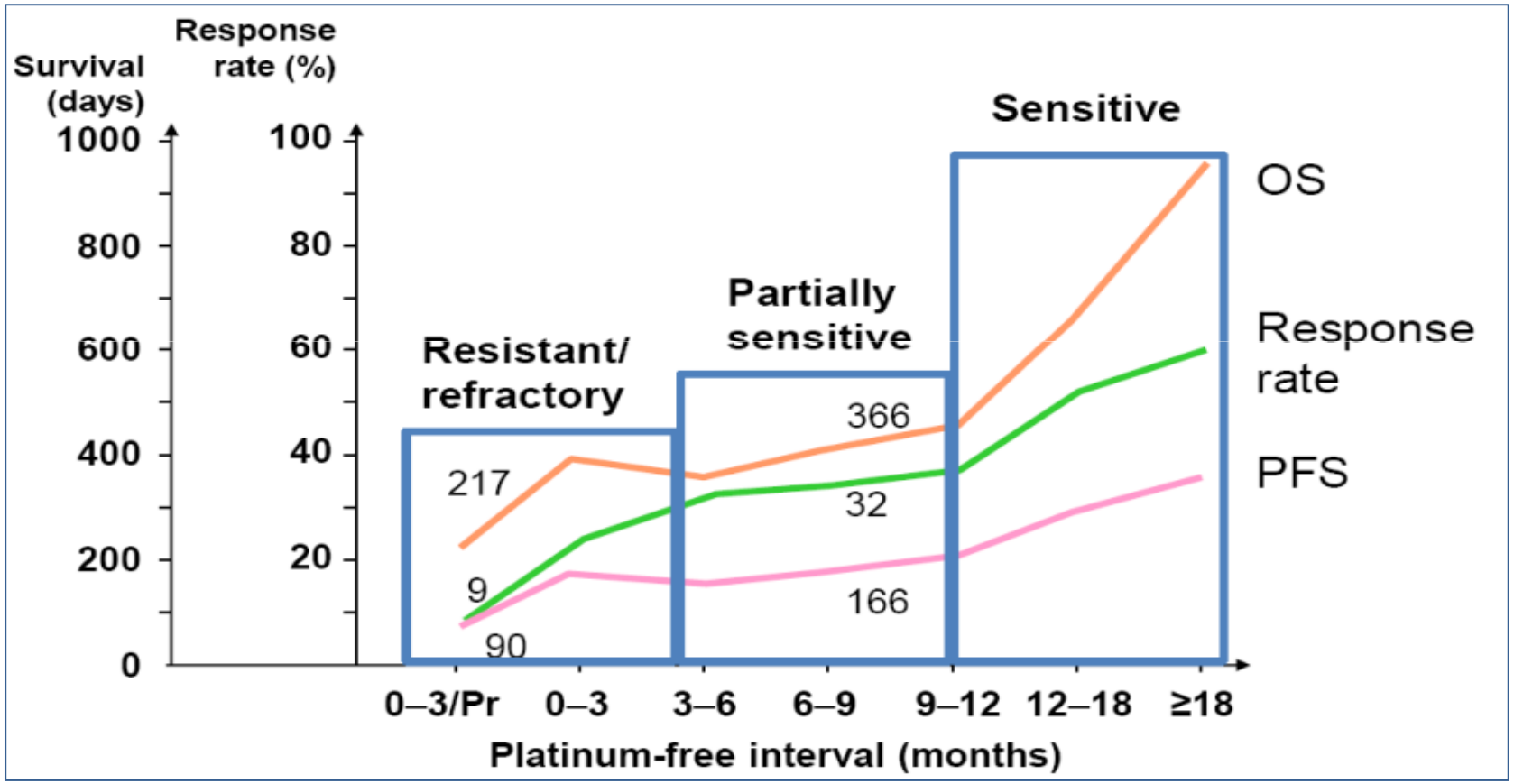


Gore, et al

Re-Traitement par protocole à base de platine

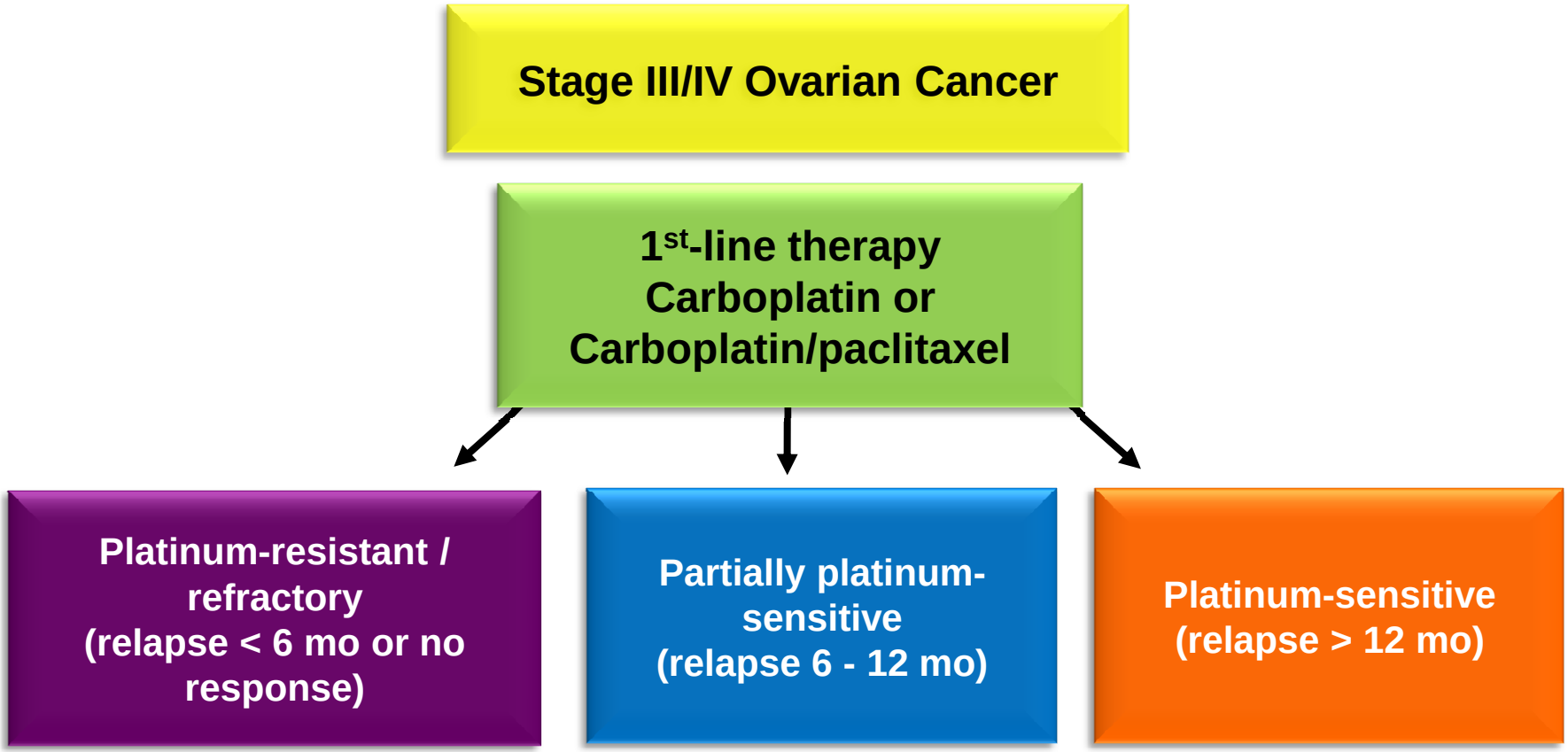
Markman M, et al. J Clin Oncol. 1991;9:389-393.
Gore ME, et al. Gynecol Oncol. 1990;36:207-211.

Relation durée d'intervalle sans sels de platine/efficacité



Pujade-Lauraine et al. J Clin Oncol 2002; 21 (Suppl): Abstract 829)

Treatment Algorithm



Resistant Disease: Available Agents

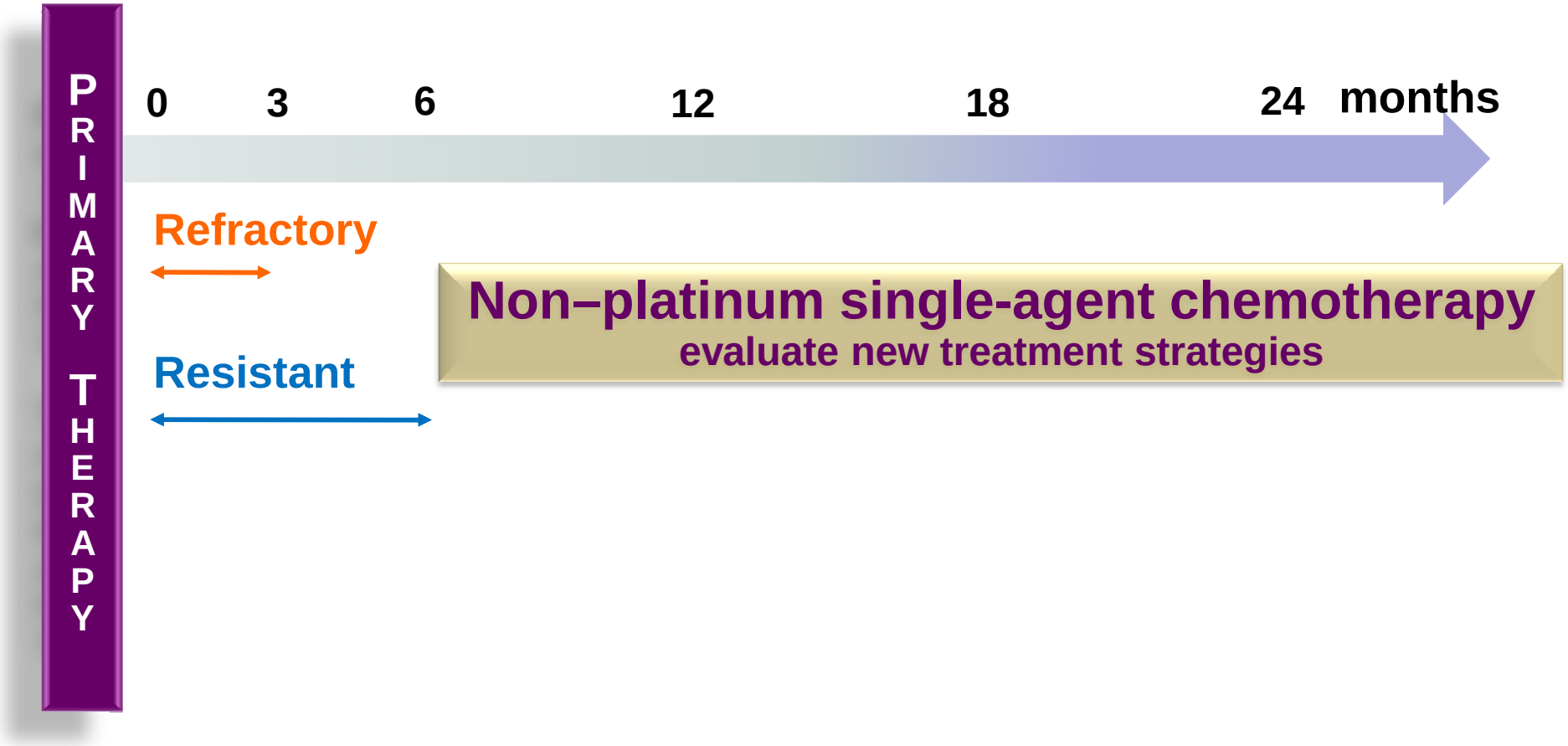
Agent	No. of Patients	Response Rate
Pegylated liposomal doxorubicin	428	18%
Topotecan	882	17%
Paclitaxel	1580	22%
Oral etoposide	234	31%
Gemcitabine	181	18%
Hexamethylmelamine	235	18%
Oxaliplatin	118	23%
Vinorelbine	71	23%

Gore M. ASCO Education Booklet. 2001.

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, 2008	No
Weekly paclitaxel (wP) vs wP + carboplatin or weekly topotecan	Gladieff et al, 2009	No

Common Treatment Approaches to ROC



Pisano et al. Ther Clin Risk Manag. 2009;5:421-426; Gadducci et al. Anticancer Res. 2001;21:3525-3533.

Meta-Analysis of Combo vs Mono: Results

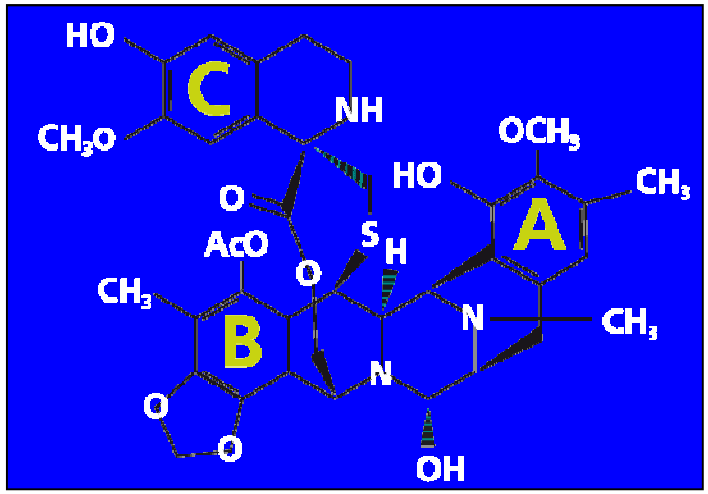
Endpoint	Odds Ratio Combo/Mono (95% CI)	P value
ORR (n=1730, 8 studies)	1.42 (1.16-1.74)	.001
PFS @ 2 years (n=2234, 7 studies)	0.67 (0.52-0.89)	.004
PFS@ 1 year	0.69 (0.57-0.84)	.000
OS @ 2 years (n=2315, 8 studies)	0.80 (0.067-0.95)	.012*

*Heterogeneity p= .002. Others NS heterogeneity.

Combination chemotherapy appears to improve ORR, PFS and OS when compared to monotherapy in the management of ROC

Orlando et al. ASCO 2007. Abstract 5524.

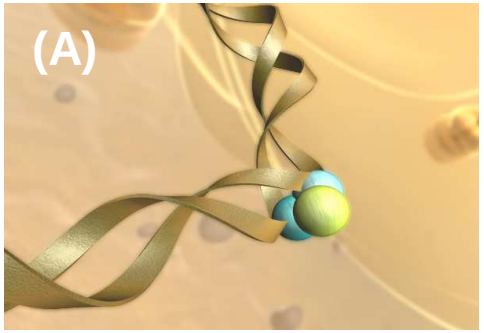
Trabectedin (Yondelis®)



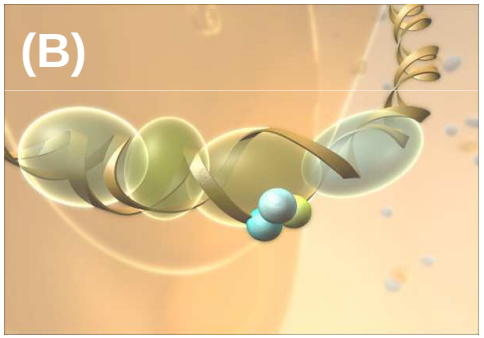
- Synthetic, marine-derived anticancer agent originally isolated from marine Caribbean tunicate, *Ecteinascidia turbinata*
- Approved in Europe for the treatment of relapsed STS
- Positive opinion of the CHMP (EMEA) to extend the indication of trabectedin + PLD in the treatment of patients with relapsed platinum-sensitive ovarian cancer (September 2009)
- Under development for prostate, breast and other cancers

Trabectedin: A Distinct Mechanism of Action

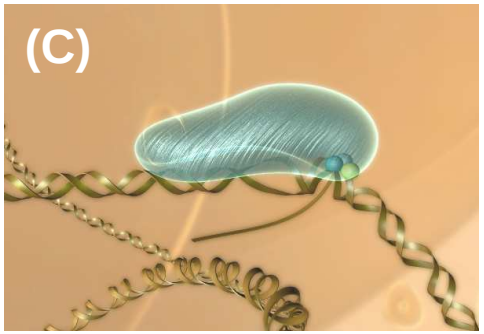
- Unique in covalently binding the minor groove of DNA and bending the double helix towards the major groove (A)



- Binding to DNA results in apoptosis after failure to repair DNA by cellular transcription coupled nucleotide excision repair (TC-NER) mechanisms (B)



- Trabectedin inhibits the transcriptional activation of certain inducible genes (C)
  - Induces cell cycle arrest at G2/M and apoptosis through a p53 independent mechanism



Pooled Analysis of 3 Phase II Trials

Study	Dose-schedule	No. Pts
Krasner *(Br. J. Cancer 2007)*	qwk 3h 0.58 mg/m²	147
Del Campo *(Ann. Oncol. 2009)*	q3wk 3h 1.3 mg/m² *vs.* q3wk 24h 1.5 mg/m²	53 53
Sessa *(JCO 2005)*	q3wk 3h 1.3 mg/m²	41

Total: 294 patients

Best Overall Response

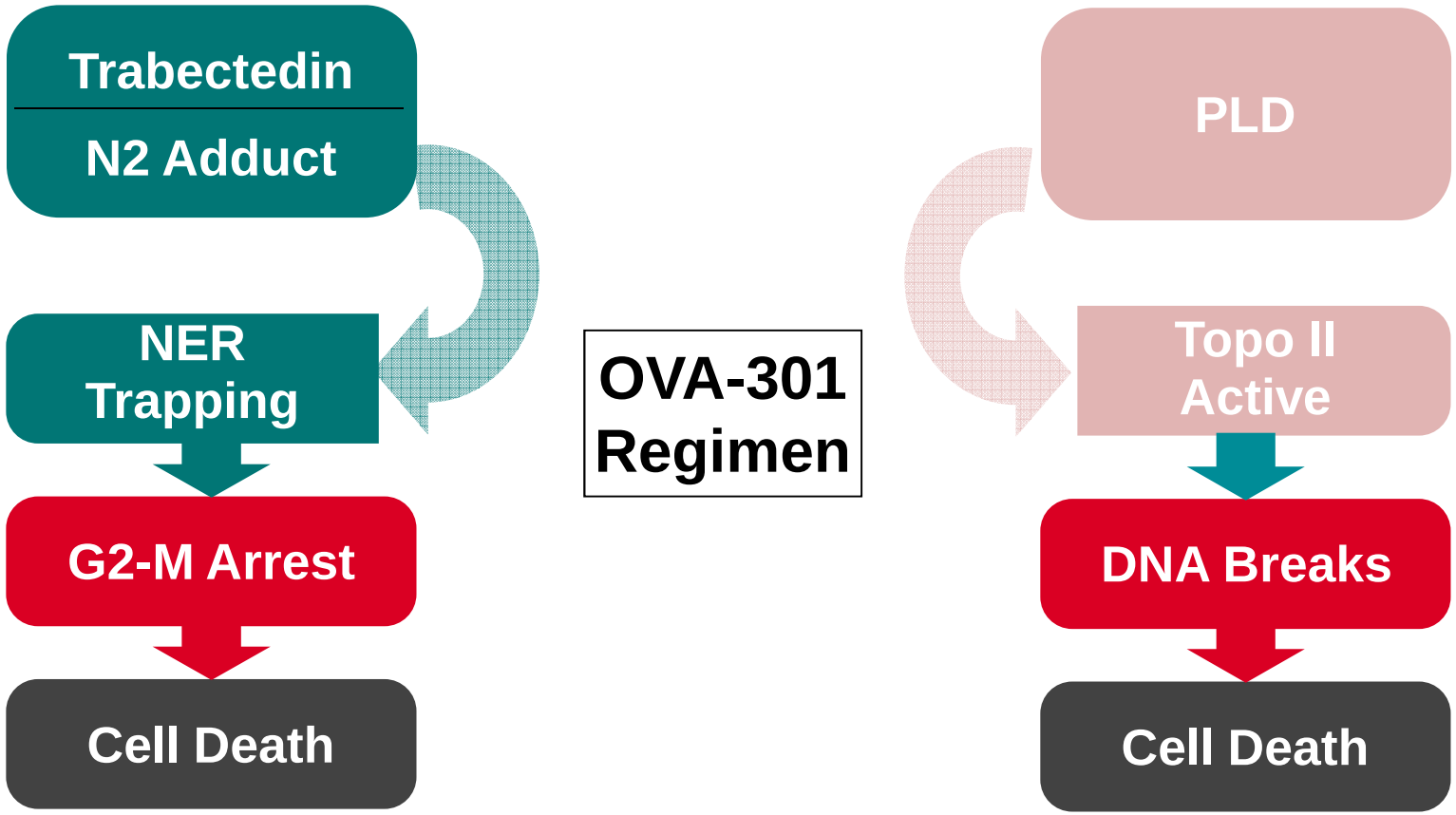
	Pt Resistant (n=107)	Pt Sensitive (n=187)
CR	0 (0%)	20 (10.7%)
PR	8 (7.5%)	48 (25.7%)
CR+PR	8 **(7.5%)** 95% CI (3.3-14.2%)	68 **(36.4%)** 95% CI (29.5-43.7%)
SD	46 (43%)	73 (39%)
PD	50 (46.7%)	38 (20.3%)
NE	3 (2.8%)	8 (4.3%)

Best Overall Response by Number of Prior Platinum-based Lines

	Platinum No. lines			
	1 line (N=199)		**≥ 2 lines (N=95)**	
	Resistant (n=67)	**Sensitive (n=132)**	**Resistant (n=40)**	**Sensitive (n=55)**
CR+PR 95% CI	**9%** 3.4-18.5	**33%** 24.7-41.3	**5%** 0.6-16.9	**46%** 32.0-59.4
SD	40%	39%	48%	40%

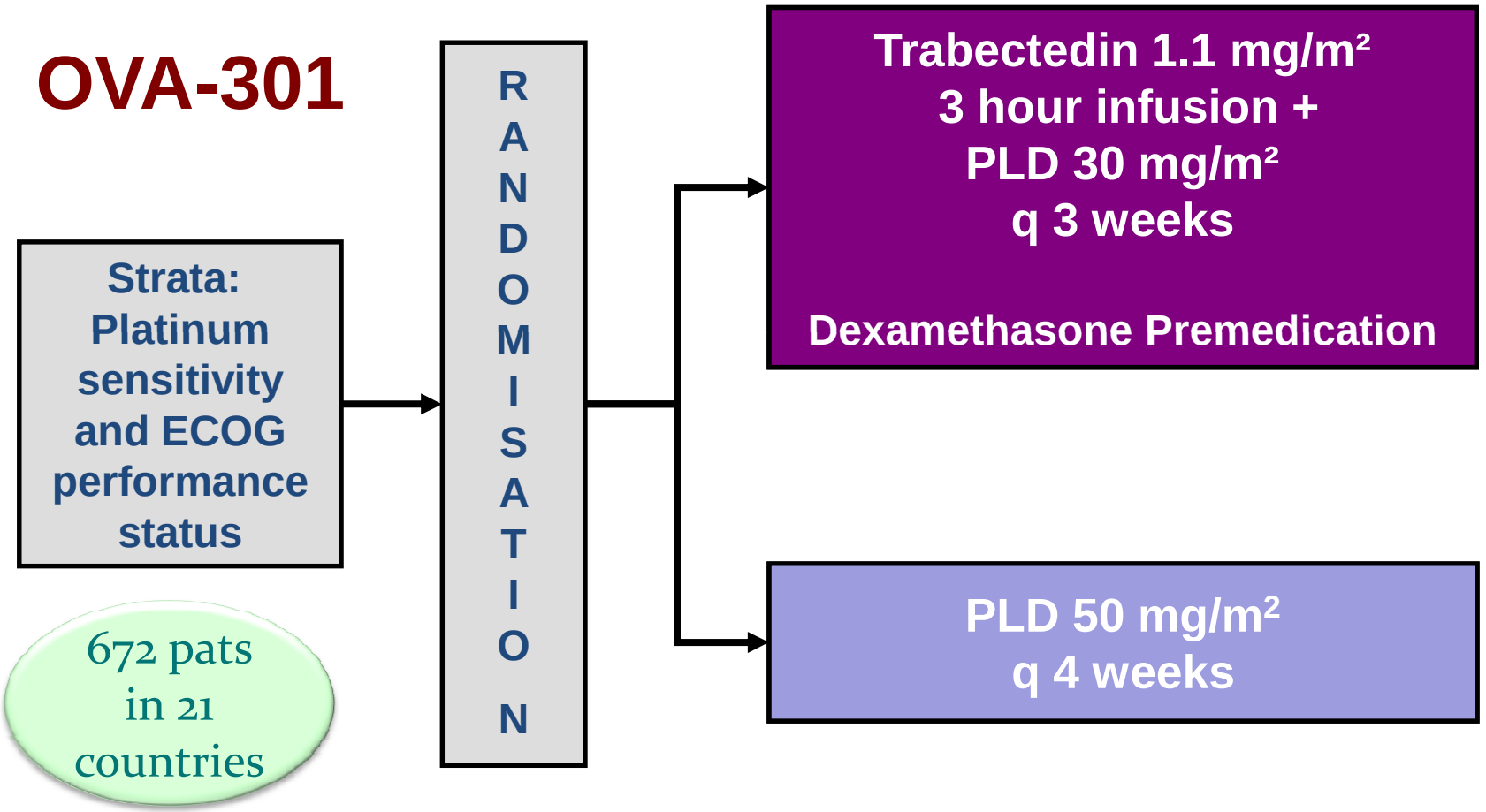
1 vs ≥2 lines in resistant population Fisher's exact test p value = 0.572
1 vs ≥2 lines in sensitive population Fisher's exact test p value = 0.0595

Unique Mechanism of Action



PLD = Pegylated Liposomal Doxorubicin

Phase III Study of Trabectedin with PLD vs PLD in Relapsed, Recurrent Ovarian Cancer



Monk et al JCO 28:3107 (2010)

PLD = Pegylated Liposomal Doxorubicin

Demographics and Baseline Characteristics

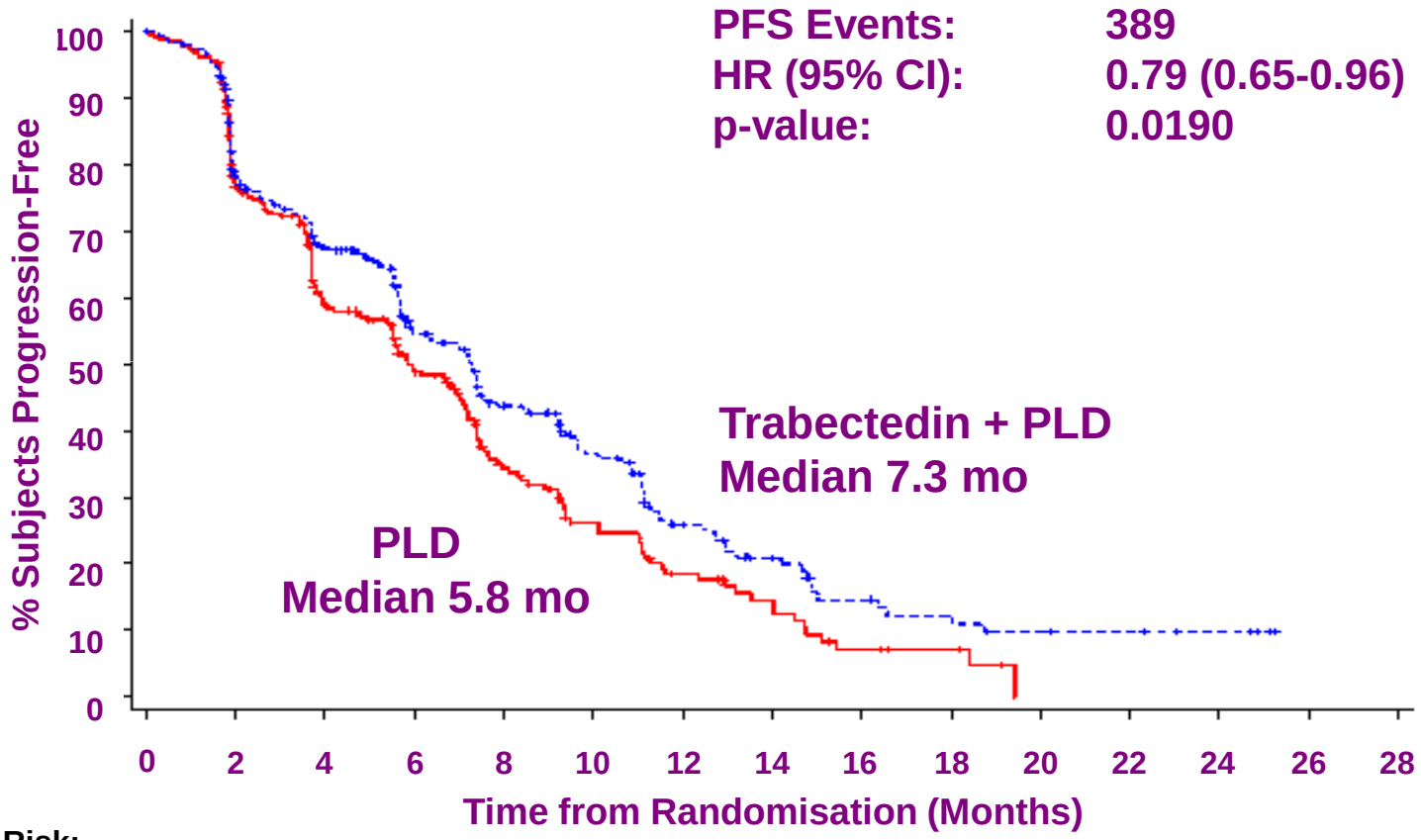
	PLD N=335	Trabectedin + PLD N=337
Race, n (%)		
White	**259 (77)**	265 (79)
Asian	**71 (21)**	66 (20)
Black	**3 (1)**	2 (1)
Other	**2 (1)**	4 (1)
ECOG performance status, n (%)		
PS 0 / 1	**324 (97)**	328 (97)
PS 2	**11 (3)**	9 (3)
Mean age (years)	**58.2**	56.8
Platinum sensitivity, n (%)		
Platinum sensitive	**212 (63)**	**218 (65)**
Platinum resistant	**123 (37)**	**119 (35)**
Mean platinum free interval (months)	**13.3**	10.6
<6 months (mo.)	**3.4**	3.9
≥6 months (mo.)	**18.9**	14.3
Prior taxanes, n (%)	**271 (81)**	269 (80)

Extent of Exposure

	PLD N=335	Trabectedin+ PLD N=337
Median total treatment duration (weeks)	**20.4**	18.7
Median no. cycles (range)	**5 (1-22)**	6 (1-21)
Patients with >6 cycles, n (%)	**79 (24)**	125 (38)
PLD dose intensity (mg/m^2/week)	**11.7**	8.3

PLD = Pegylated Liposomal Doxorubicin

PFS Final Analysis - Independent Radiology

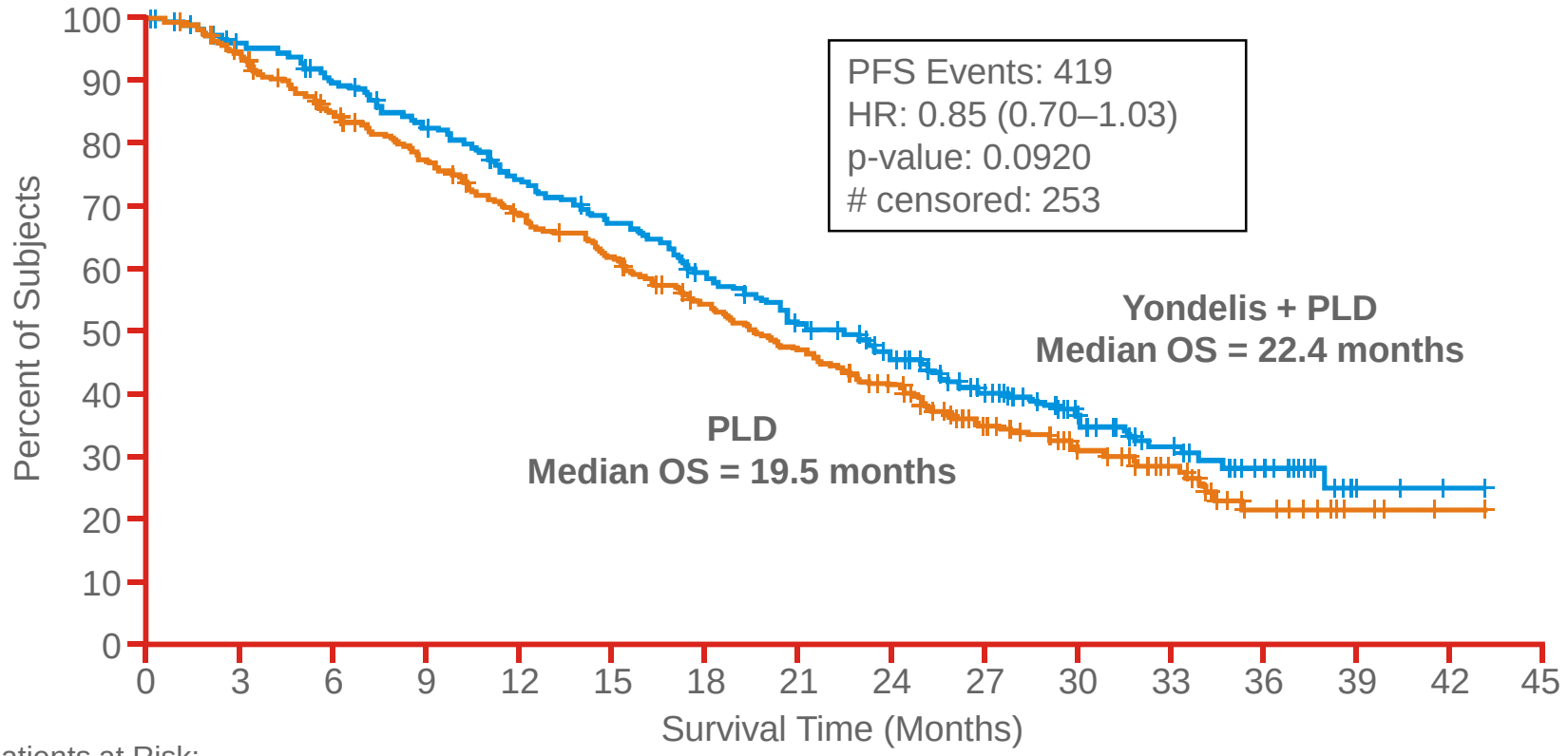


Subjects at Risk:															
PLD	317	208	139	93	54	35	22	14	6	4	0	0	0	0	0
Trabectedin + PLD	328	225	176	121	86	63	33	22	13	10	7	6	4	0	0

PLD = Pegylated Liposomal Doxorubicin

Overall Survival (2nd Interim Analysis, May 2009)

All Randomised Patients



Patients at Risk:

PLD	335	309	271	243	211	190	162	140	117	71	47	29	13	4	1	0
Yondelis + PLD	337	312	291	266	238	214	187	159	133	90	54	35	21	3	1	0

Poveda A et al. Annals of Oncology 2010

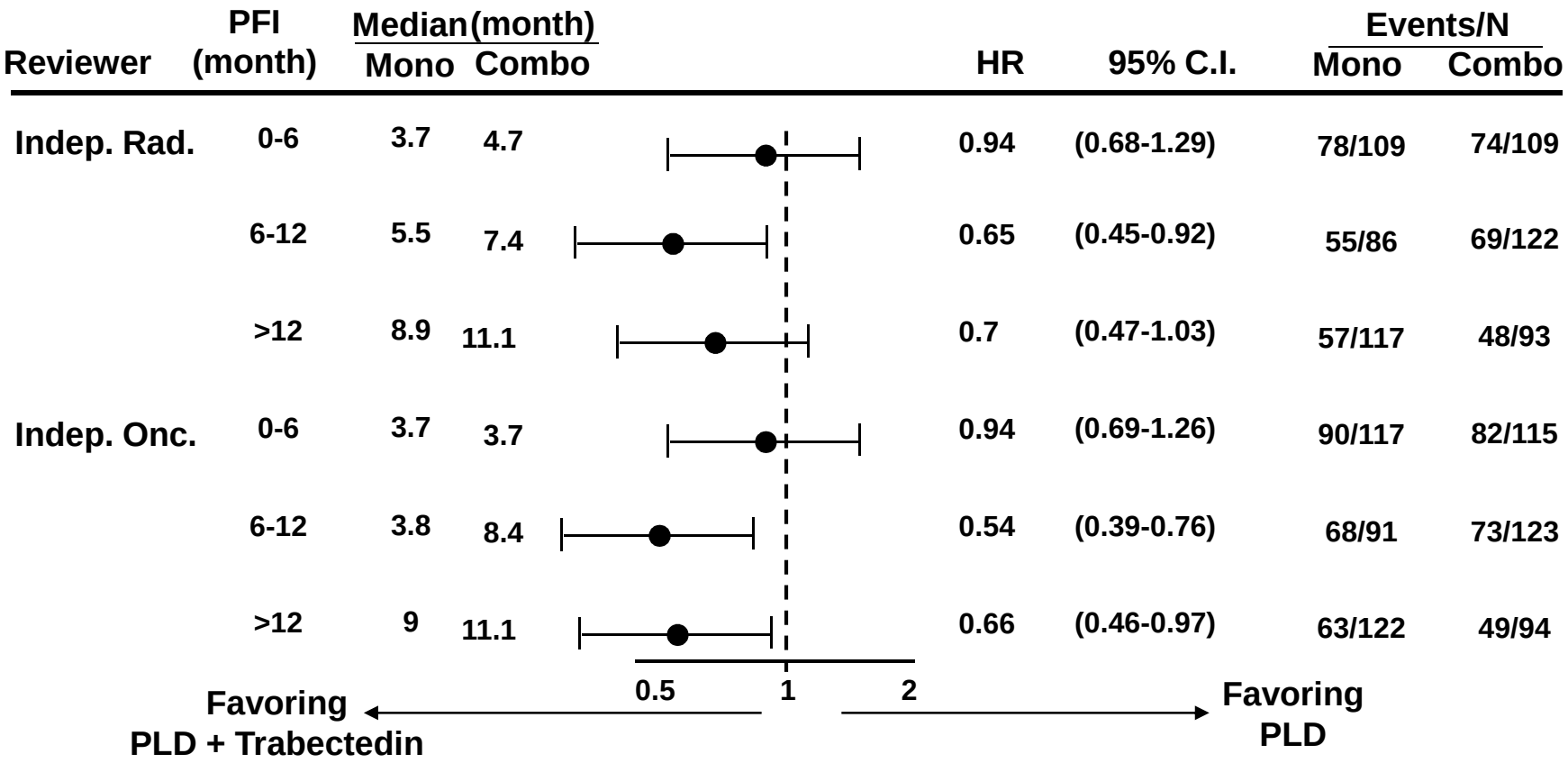
OVA-301: Best Overall Response*
(by platinum sensitivity)

	PLD N=335*	Trabectedin+PLD N=337*	p-value
Platinum Resistant	ORR**	ORR**	
Independent Radiology	**12.2%**	**13.4%**	**0.85**
Investigator	**16.3%**	**22.7%**	**0.26**
Platinum Sensitive			
Independent Radiology	**22.6%**	**35.3%**	**0.0042**
Investigator	**32.5%**	**47.2%**	**0.0022**

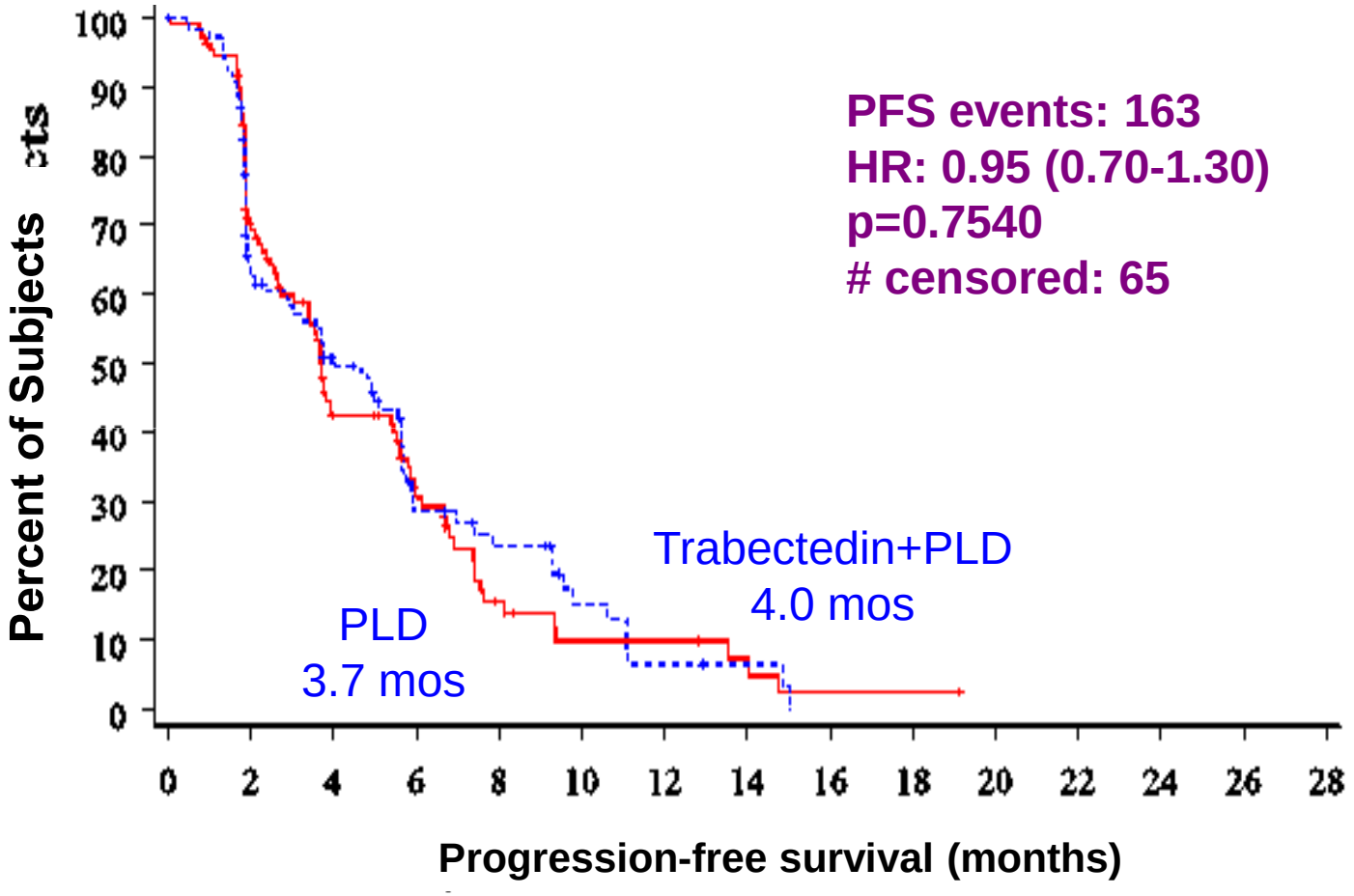
*All randomized subjects
**ORR= Overall response rate

PFS Final Analysis – by stratification group

Hazard Ratio and 95% Confidence Interval

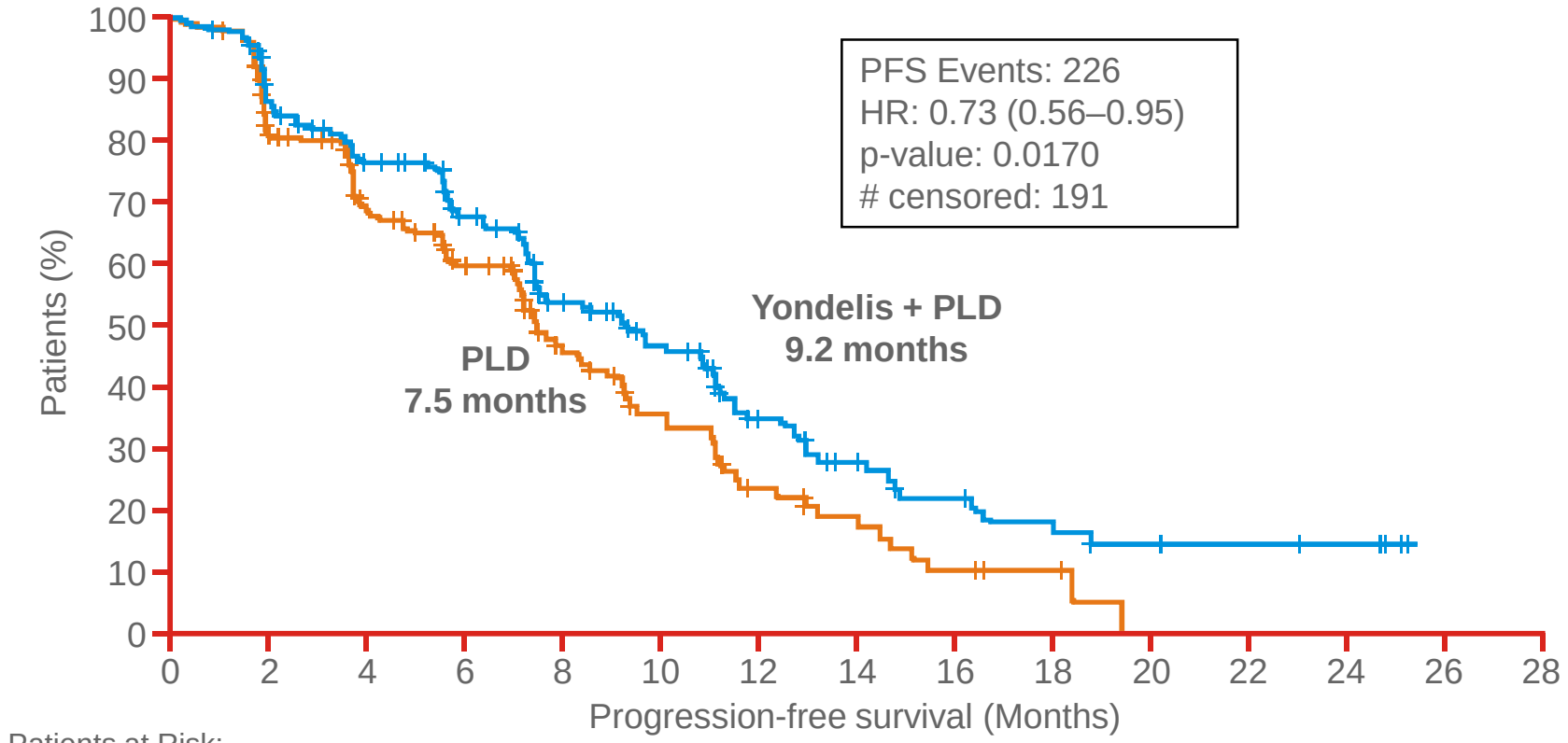


PFS - Platinum Resistant Stratum (PFI < 6 mo) (n=228)



No. Subjects at Risk															
PLD	115	70	37	22	9	5	5	3	1	1	0	0	0	0	0
Trabectedin/PLD	113	61	43	19	14	7	3	2	0	0	0	0	0	0	0

PFS – Platinum Sensitive Stratum (PFI ≥6 months) Independent Radiology (n=417)



Patients at Risk:

PLD	202	138	102	71	45	30	17	11	5	3	0	0	0	0	0
Yondelis + PLD	215	164	133	102	72	56	30	20	13	10	7	6	4	0	0

Monk BJ et al. J Clin Oncol 2010; 28:3107–14

Analysis Of The Partially Platinum-sensitive (PFI 6–12 Months) Subpopulation of the OVA-301 Trial

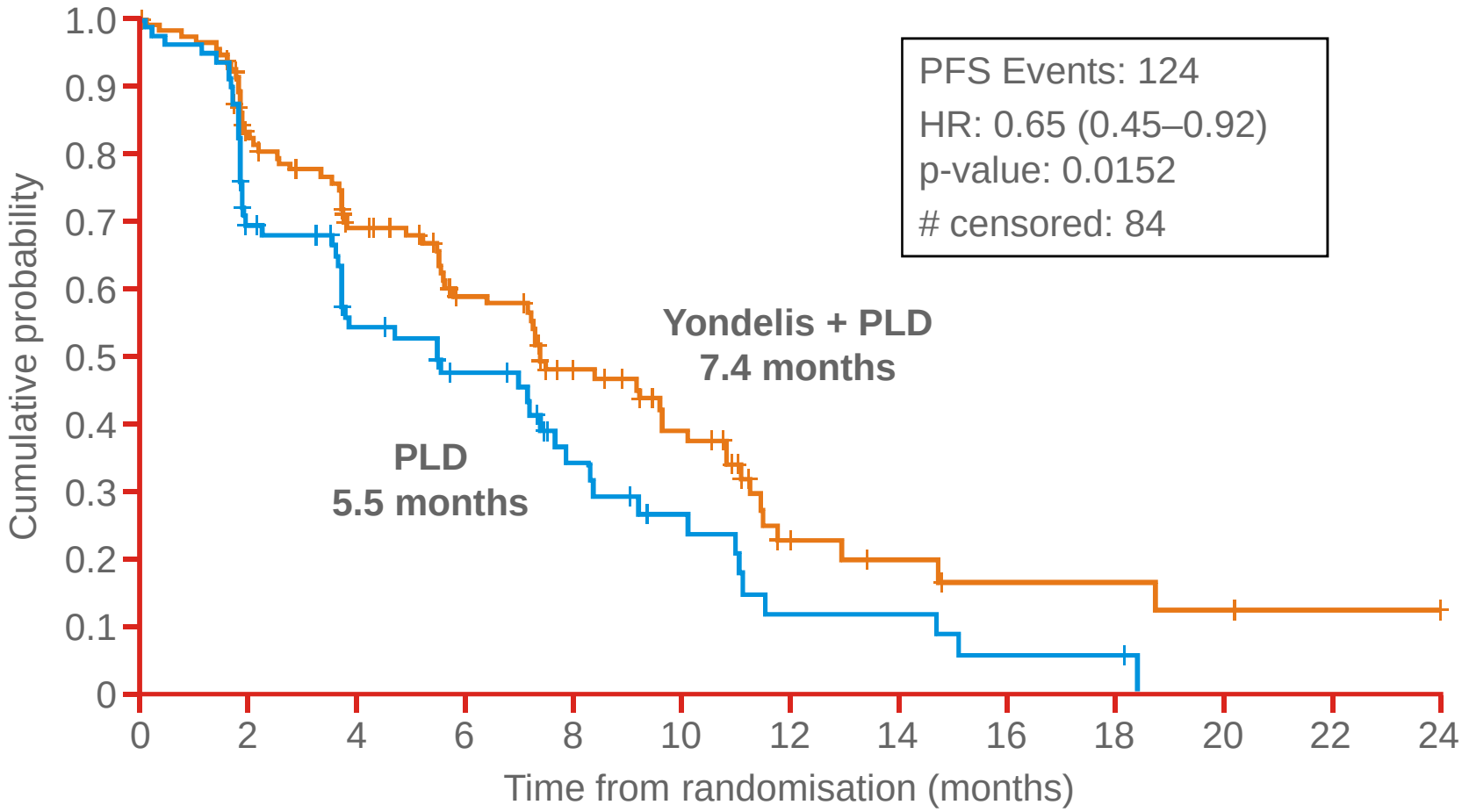
original article

Annals of Oncology
doi:10.1093/annonc/mdq352

Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6–12 months) subpopulation of OVA-301 phase III randomized trial

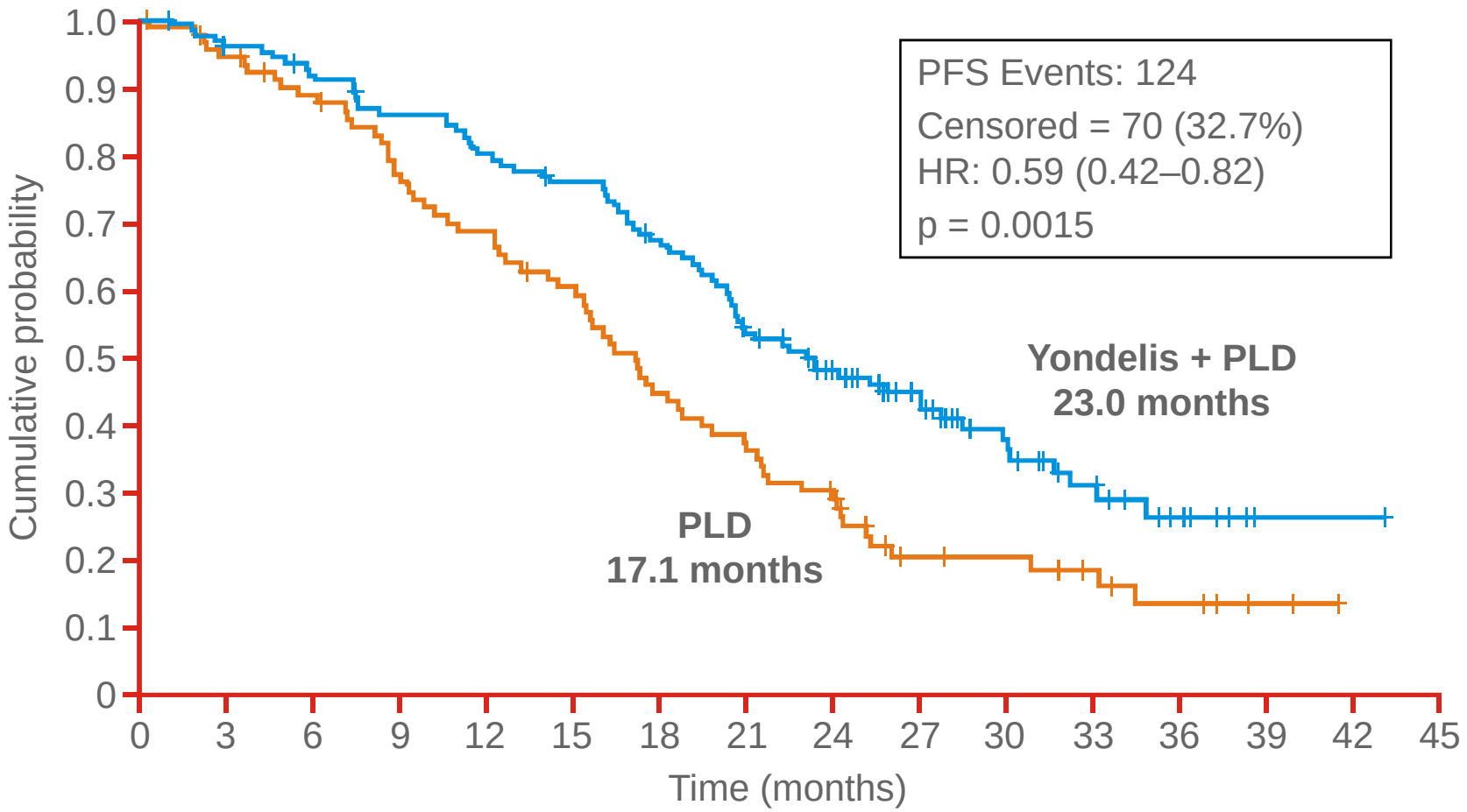
A. Poveda[1*], I. Vergote[2], S. Tjulandin[3], B. Kong[4], M. Roy[5], S. Chan[6], E. Filipczyk-Cisarz[7], H. Hagberg[8], S. B. Kaye[9], N. Colombo[10], C. Lebedinsky[11], T. Parekh[12], J. Gómez[11], Y. C. Park[12], V. Alfaro[11] & B. J. Monk[13]

PFS – Intermediate Sensitivity (PFI 6–12 mo) Independent Radiology (n=208)



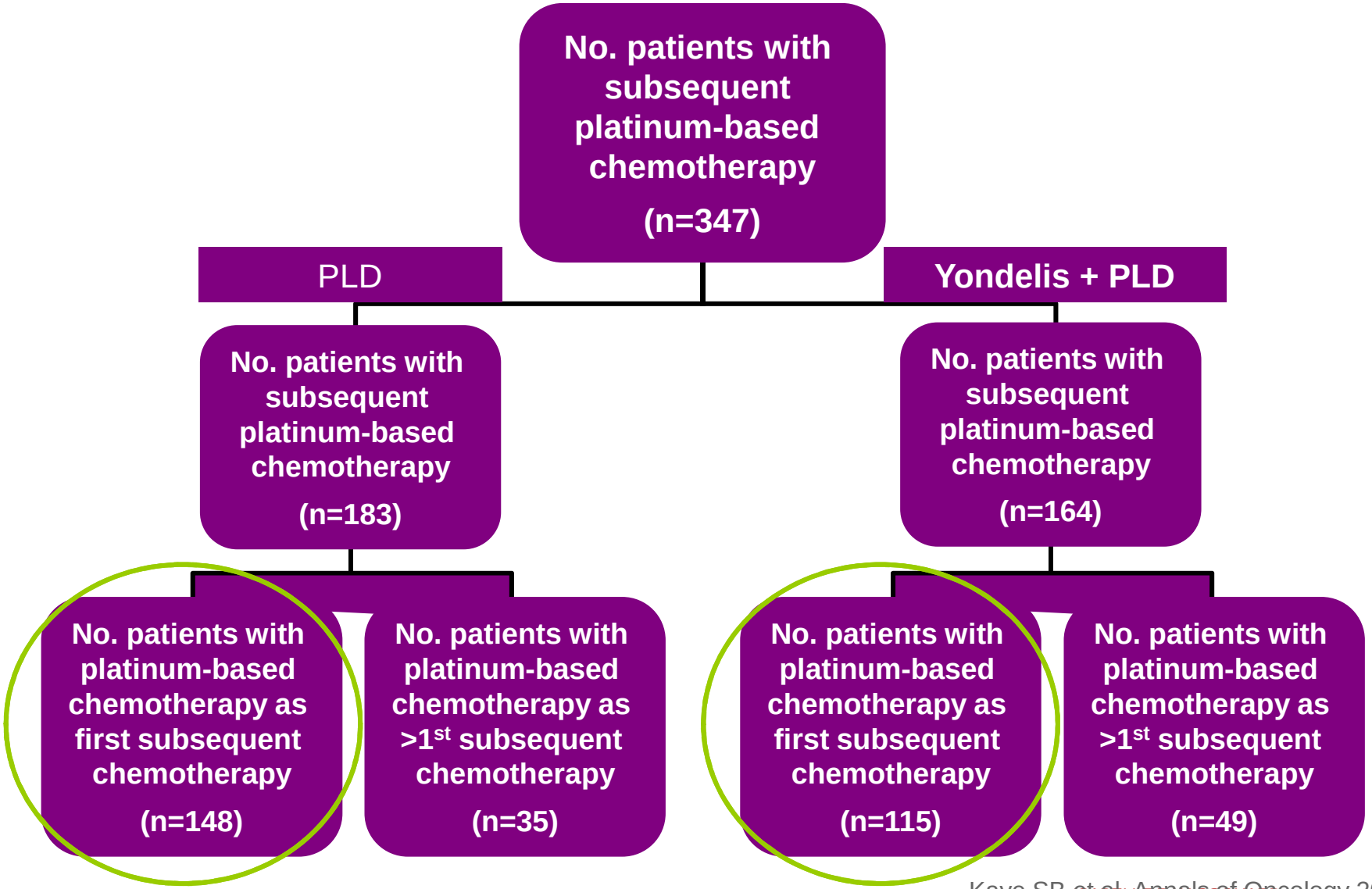
Poveda A et al. Annals of Oncology 2010

OS – Intermediate Sensitivity (PFI 6-12 mo)



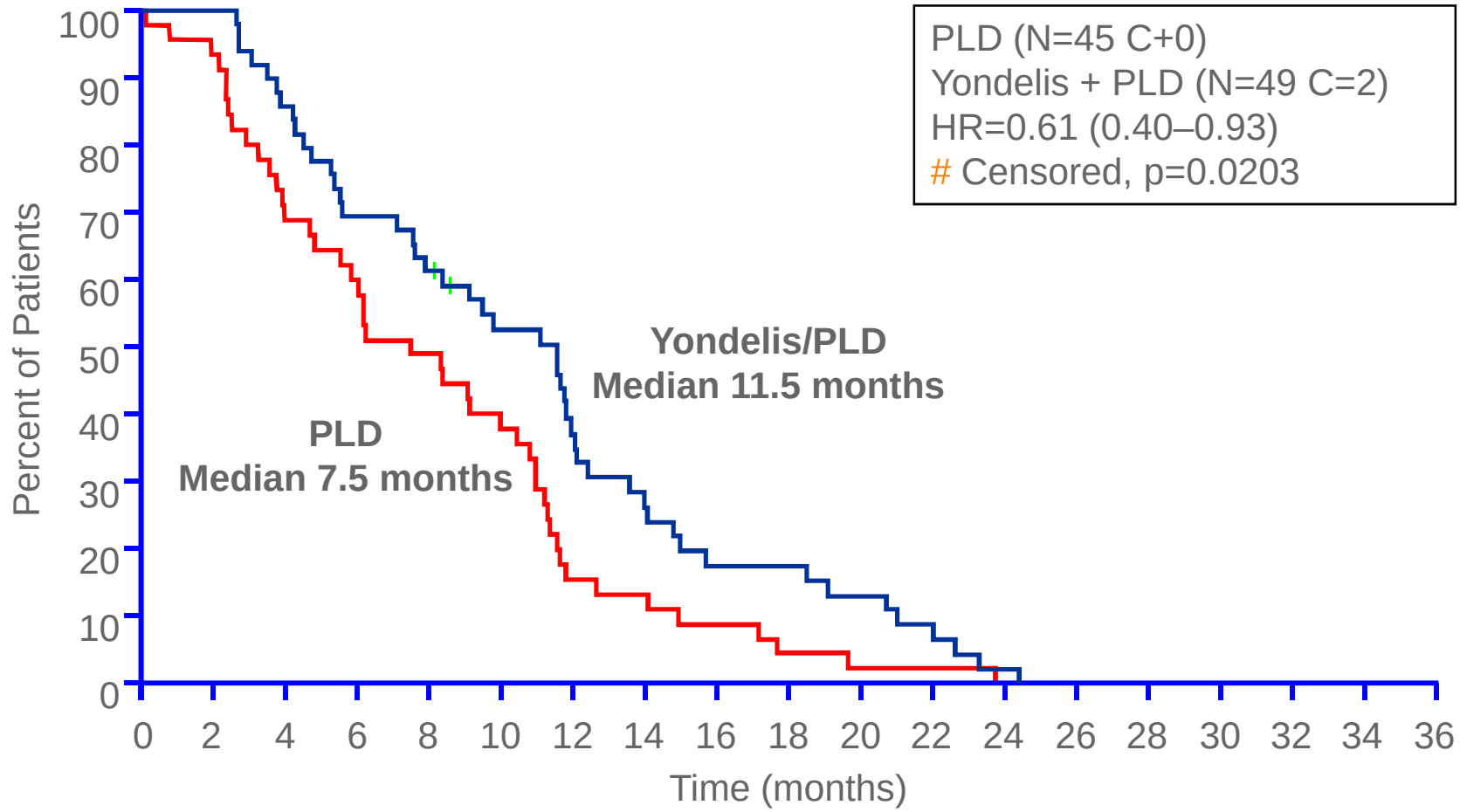
Poveda A et al. Annals of Oncology 2010

Flow Chart of Patients Receiving Platinum as Further Chemotherapy



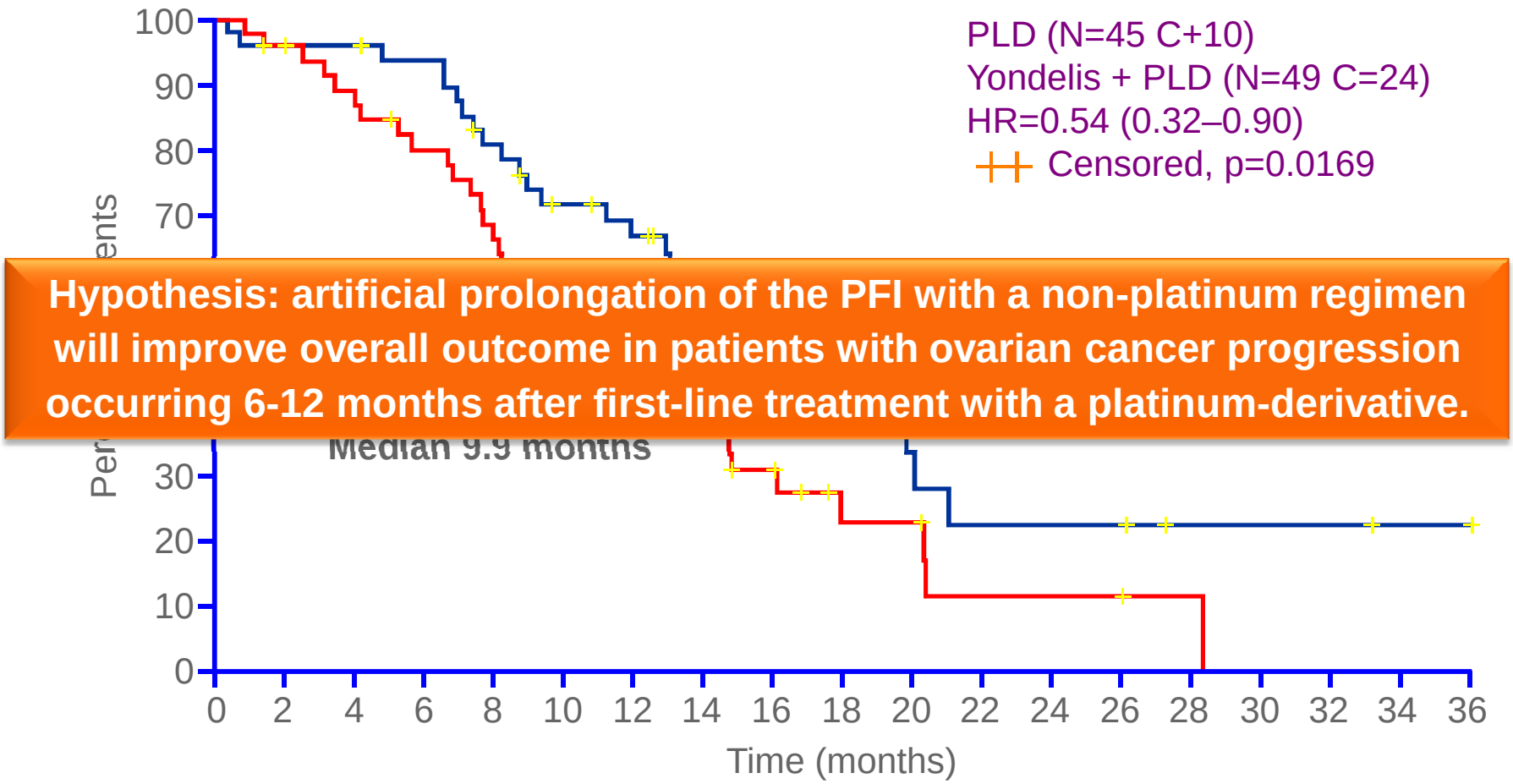
Kaye SB et al. Annals of Oncology 2010

Time from Randomisation to Subsequent Platinum given as 1st Option Immediately after OVA-301 (PLD or PLD + Yondelis)



Kaye SB et al. Annals of Oncology 2010

Survival from Subsequent Platinum Given as 1st Option Immediately after OVA-301



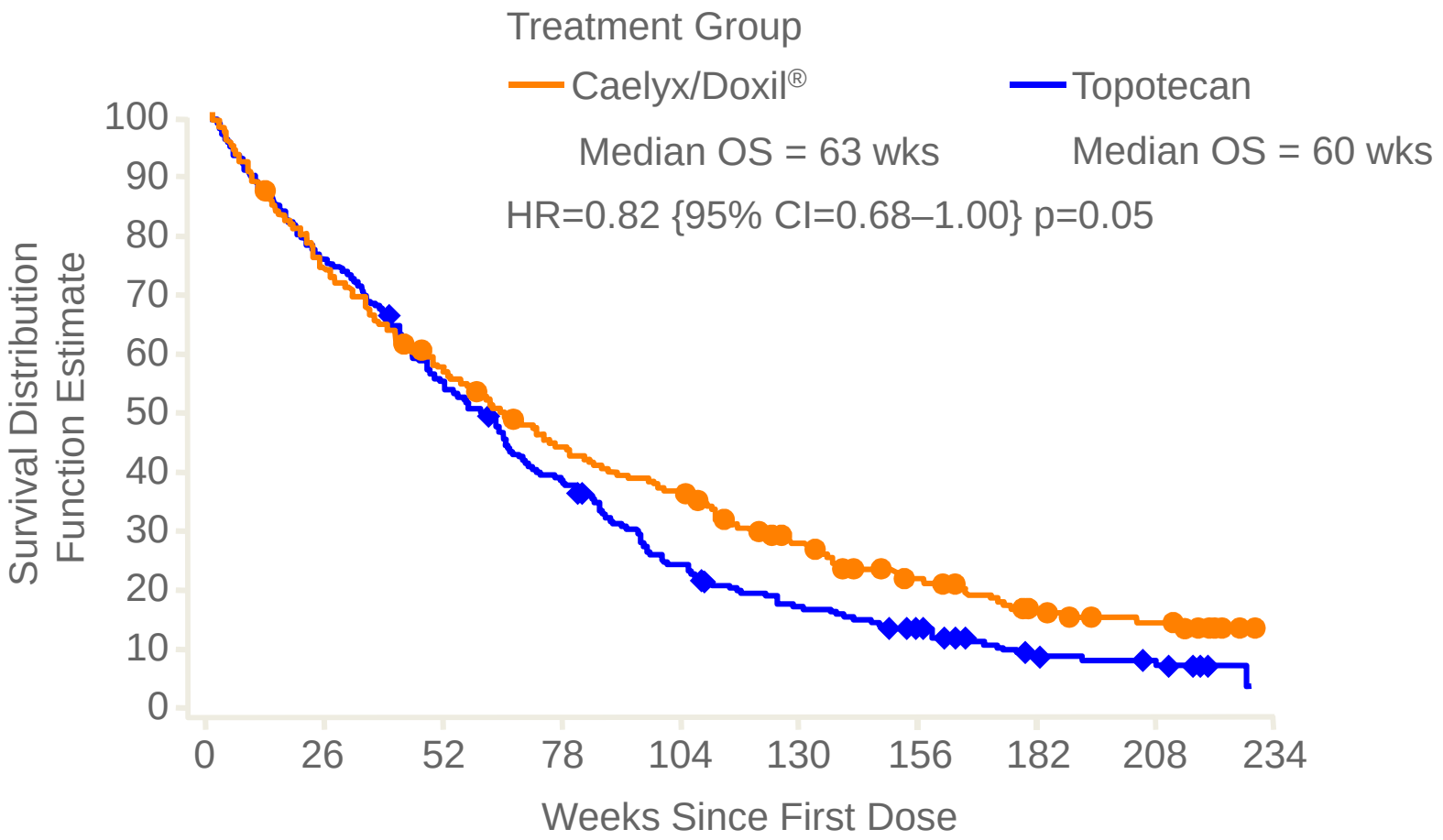
Hypothesis: artificial prolongation of the PFI with a non-platinum regimen will improve overall outcome in patients with ovarian cancer progression occurring 6-12 months after first-line treatment with a platinum-derivative.

Kaye SB et al. Annals of Oncology 2010

Treatment Options for Partially Platinum-Sensitive Relapse

- Is a non-platinum drug an alternative?
- Is the difference between the two non-platinum drugs due to positive effects of one treatment on subsequent treatment?
- Can partial platinum-sensitivity be increased by delaying re-introduction platinum?

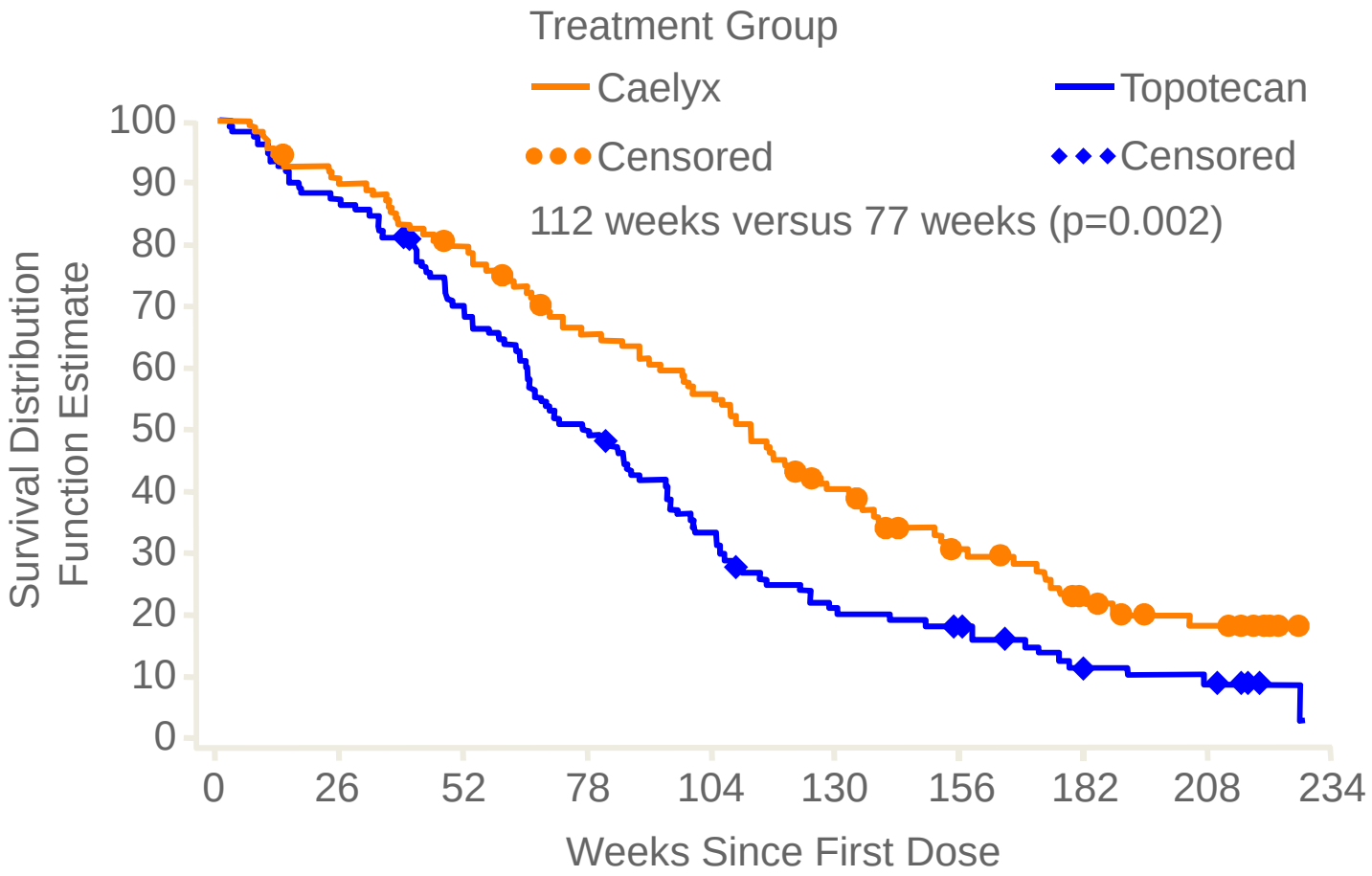
Pegylated Liposomal Doxorubicin vs. Topotecan



HR = hazard ratio; CI = confidence interval

Gordon AN et al. Gynecol Oncol 2004;95:1–8

PLD vs. Topotecan: Overall Survival – Platinum Sensitive Group



Response to Re-introduction of Platinum Treatment

Platinum in second line

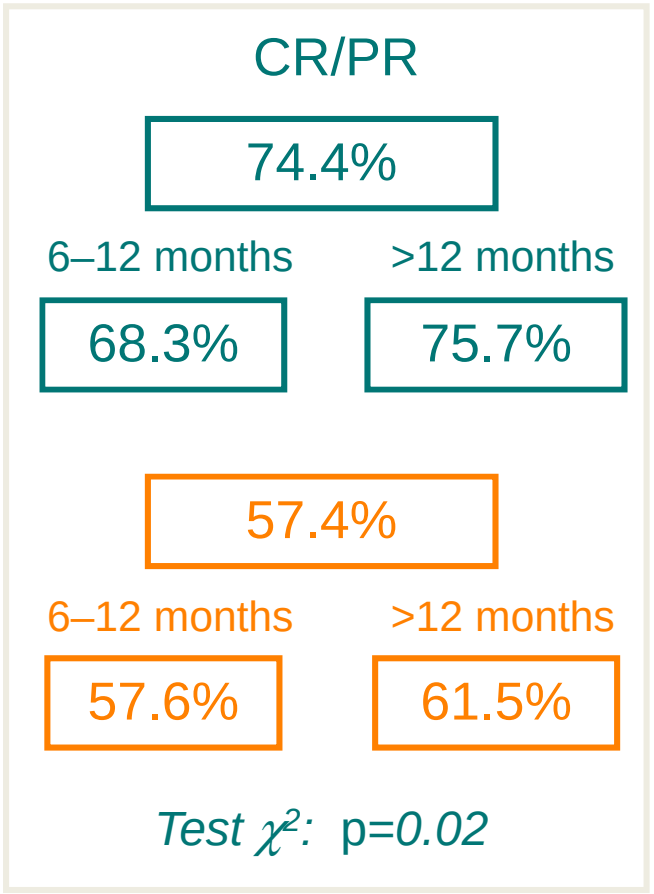
RFI 19 months

PFI 20 months

Platinum in following lines

RFI 9.6 months

PFI 23 months



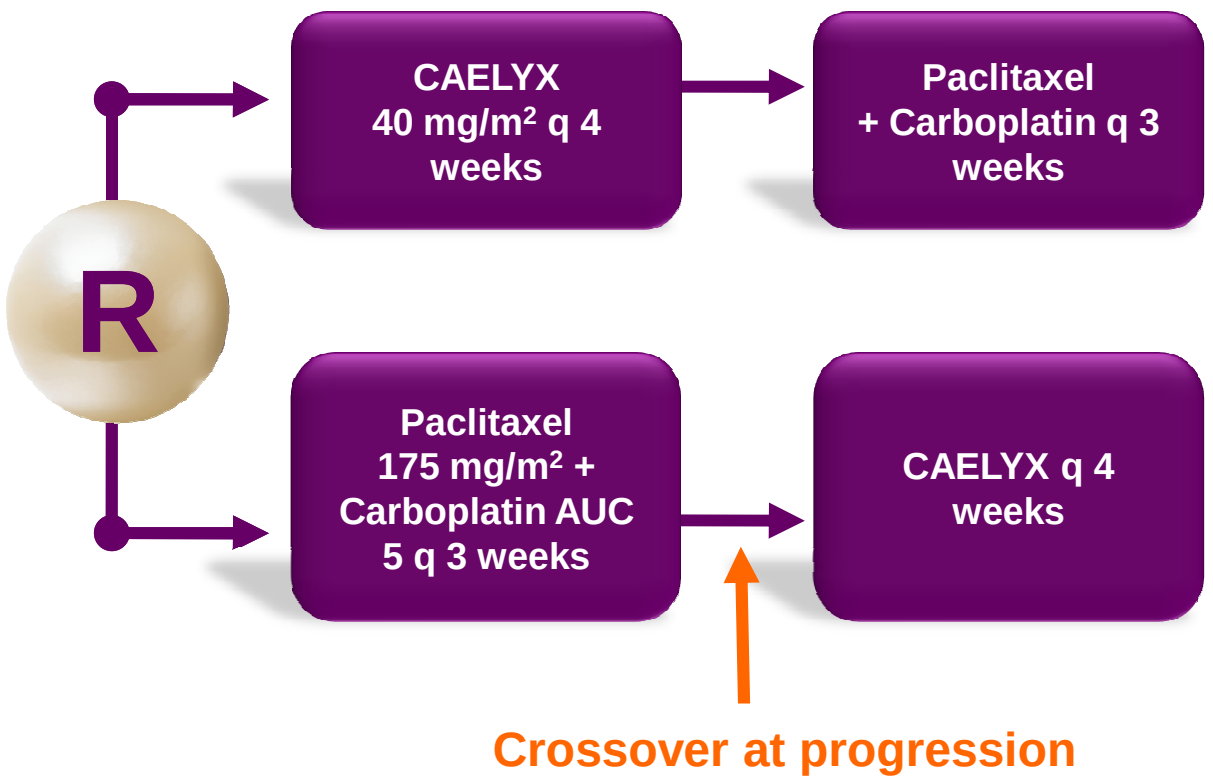
RFI = recurrence-free interval;
PFI = progression-free interval

Pignata et al.Oncology 2006;71:320–326

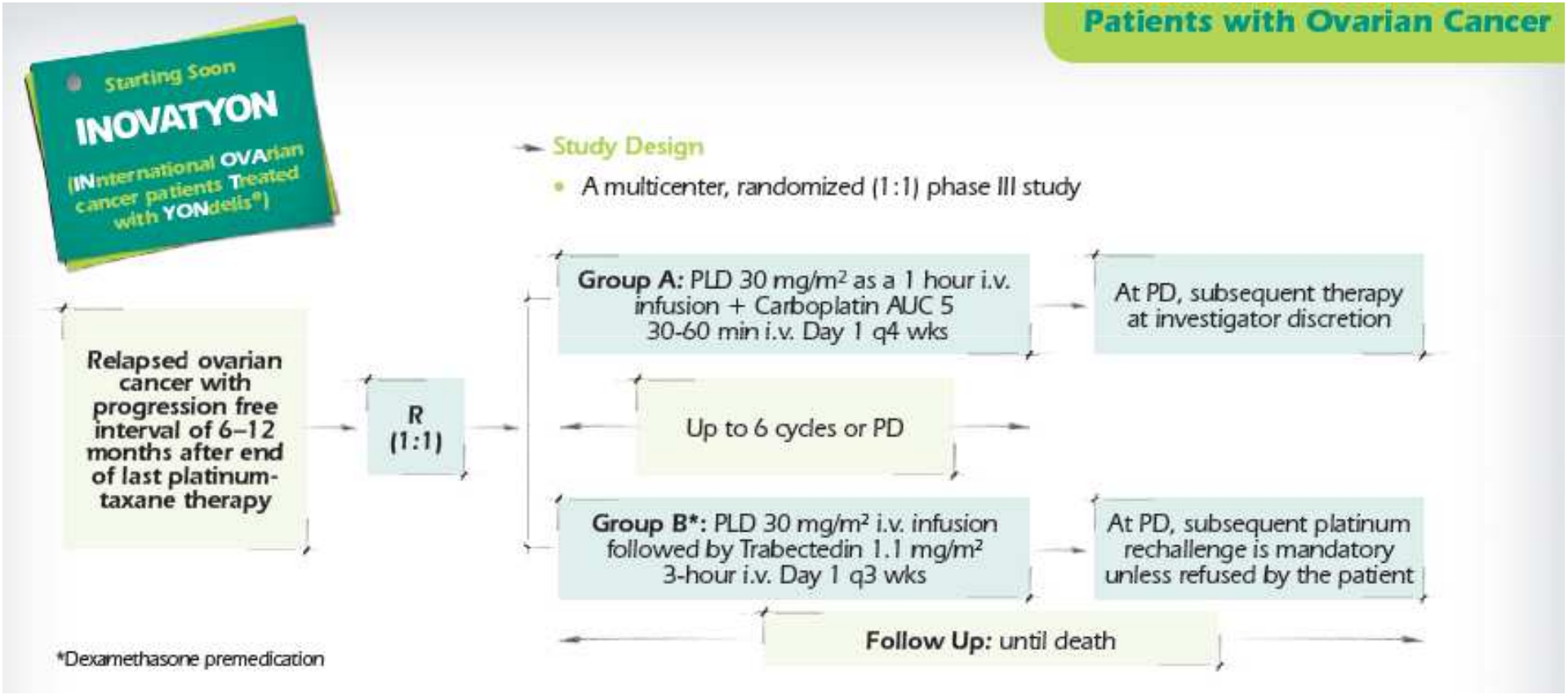
CAELYX in Partially Platinum-Sensitive Ovarian Cancer: *MITO-8 Trial*

Enrollment

- Disease recurrence between 6 and 12 months after a first-line platinum based therapy
- No more than 2 previous lines of previous therapy



INOVATYON Design



Dose Modification due to Drug Related AE

	PLD N = 330	Trab + PLD N = 333
Cycle delay Total	40%	68%
ANC*	**18%**	**53%**
HFS**	**12%**	**4%**
Dose reduction	39%	Trab: 38% PLD: 39%

*ANC = Absolute neutrophil count
**HFS = Hand foot syndrome

OVA-301: Selected Adverse Events (%)

	PLD (N=330)*		Trab + PLD (N=333)*	
	Grade 3	Grade 4	Grade 3	Grade 4
Hand-foot syndrome	18%	1%	4%	0%
Mucositis/Stomatitis	11%	<1%	3%	0%
Cardiac disorders	<1%	<1%	2%	<1%
Fatigue	5%	<1%	8%	<1%
Vomiting	4%	0%	12%	<1%
Nausea	4%	0%	10%	0%
Febrile neutropenia	2%	<1%	6%	2%
Neuropathy	0%	0%	<1%	0%
Alopecia (≥Grade 2)	4%		2%	

* Number treated

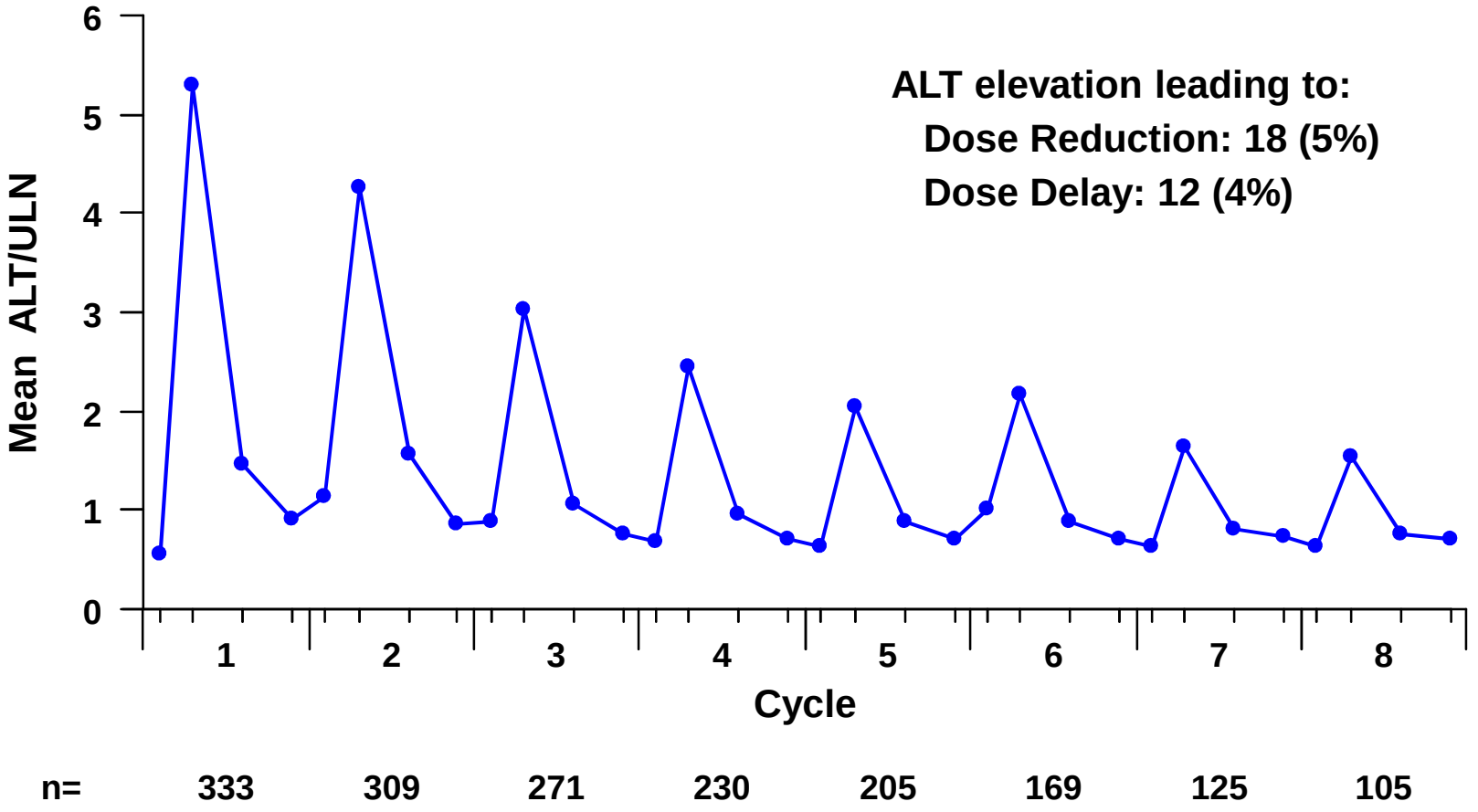
NCI CTC Version 3.0

OVA-301 Grade 3/4 Laboratory Abnormalities

		PLD (N=330)		Trab + PLD (N=333)	
		Grade 3	Grade 4	Grade 3	Grade 4
Hematology	**Neutrophils**	**20%**	**10%**	**30%**	**42%**
	WBC	**16%**	**4%**	**45%**	**18%**
	Platelets	**2%**	**2%**	**12%**	**11%**
	Hemoglobin	**6%**	**2%**	**13%**	**6%**
Biochemistry	**ALT increase**	**2%**	**0%**	**46%**	**5%**
	AST increase	**1%**	**<1%**	**12%**	**2%**
	CPK increase	**0%**	**0%**	**1%**	**1%**
	Alk. Phosphatase	**1%**	**0%**	**2%**	**0%**
	Bilirubin	**<1%**	**0%**	**<1%**	**0%**
	Creatinine	**1%**	**0%**	**<1%**	**<1%**
Transfusions	**Blood**	**12%**		**11%**	
	Platelet	**2%**		**10%**	

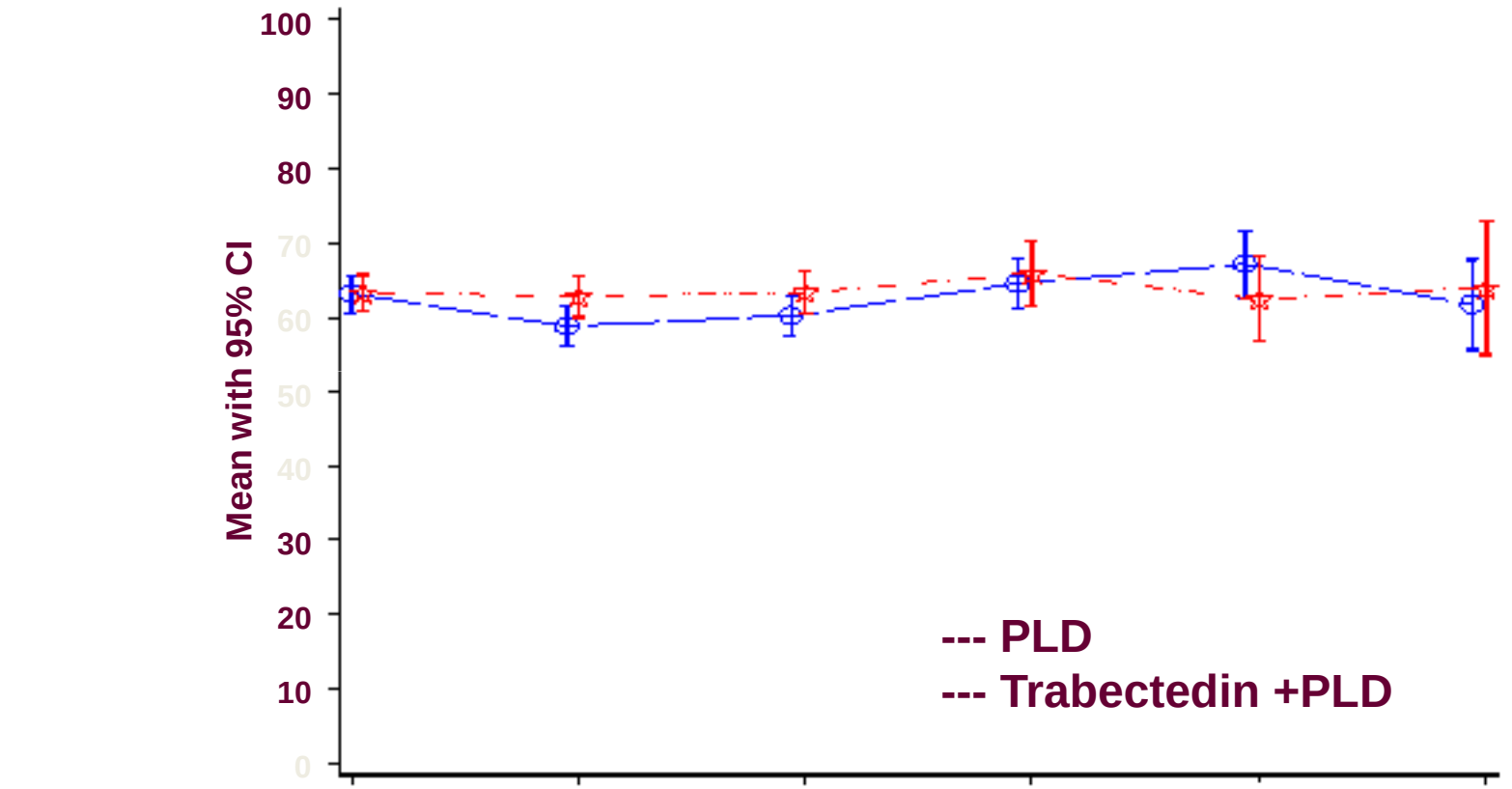
NCI CTC Version 3.0

Mean ALT in All Patients During Treatment With Trabectedin + PLD



OVA-301: QLQ-C30 Global Health Status Scale

Mean Score Over Time – All Randomised Subjects



N	Baseline	C3	C5	C7	C9	C11
PLD	303	209	159	71	42	22
Trabectedin + PLD	312	236	182	109	61	41

Krasner CN et al ASCO 2009 abst 5526

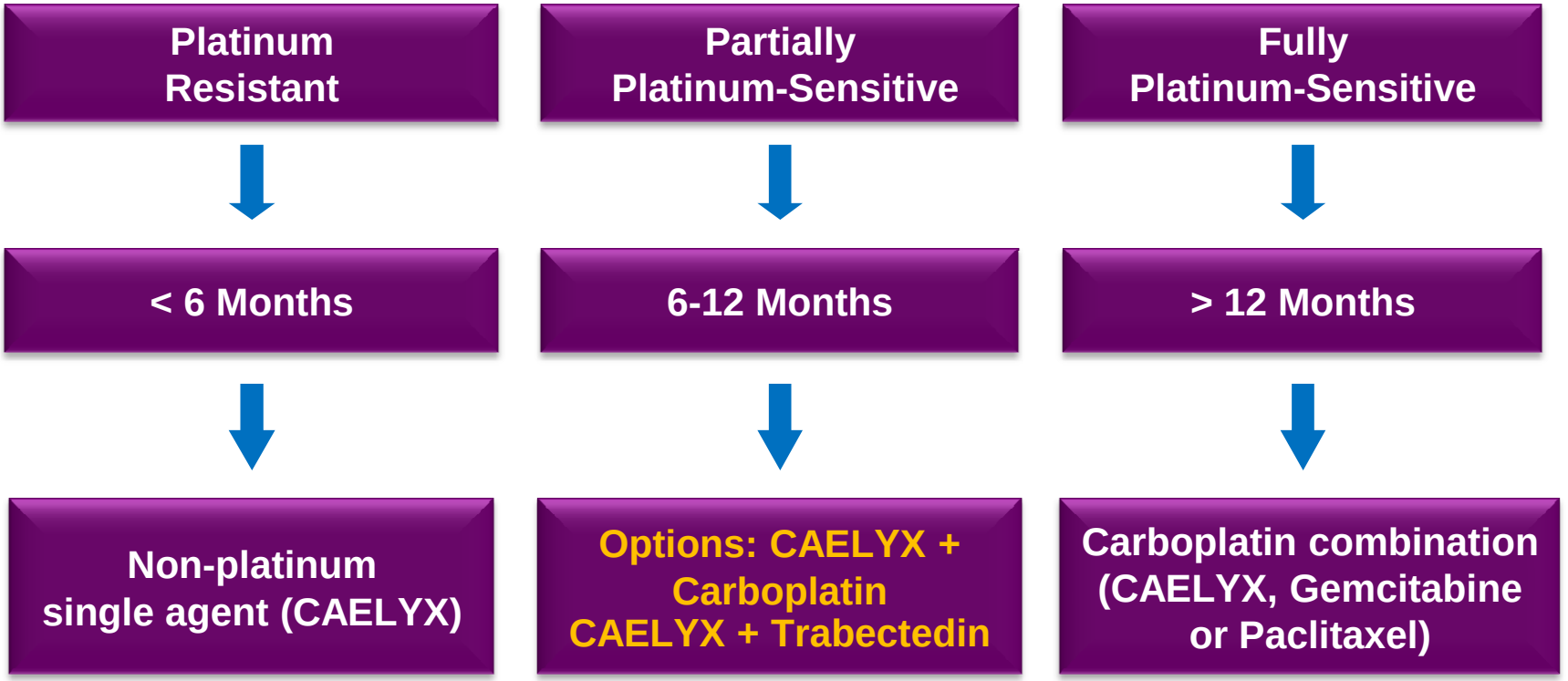
Safety of T+PLD *vs* Standard Combinations

Grade 3-4 toxicities	Paclitaxel + platinum **(n=392)**	Gemcitabine + carboplatin **(n=175)**	Carboplatin + PLD (CALYPSO) **(n=464)**	Trabectedin + PLD (OVA-301) **(n=333)**
Hematological				
Anaemia	**29% (Events leading to dose modification)**	**27%**	**8%**	**19%**
Febrile neutropenia		**1%**	**2%**	**8%**
Neutropenia		**70%**	**35%**	**72%**
Thrombocytopenia		**35%**	**16%**	**23%**
Non-hematological				
Alopecia (grade ≥ 2)	**86%**	**14%**	**7%**	**2%**
Allergy / HSR	**NR**	**2%**	**2%**	**<1%**
ALT increase	**NR**	**NR**	**NR**	**51%**
Fatigue	**NR**	**2%**	**7%**	**8%**
Mucositis	**7% (G 2-3)**	**NR**	**2%**	**1%**
Neuropathy	**20% (G 2-4)**	**1%**	**1%**	**<1%**
Vomiting	**35% (G 2-4 including nausea)**	**3%**	**4%**	**12%**

Phase III positive studies: Plat Sensitive Patients

	Platinum ± Paclitaxel (ICON-4) Parmar *et al.*	**Carboplatin ± Gemcitabine Pfisterer *et al.***	**Carboplatin+ PLD (Calypso) Pujade Lauraine *et al.***	**PLD ± Trabectedin (OVA-301: Plat Sens)**
N	802	356	976	430
1° endpoint	OS	PFS	PFS	PFS
Prior taxane	40%	71%	99%	77%
PFI 6-12 mo.	25%	40%	35%	50%
Risk of progression	**↓ 24%**	**↓ 28%**	**↓ 18%**	**↓ 27% / 38%**
Risk of death	↓ 18%	No ↓	NA	NS ↓41 % (6-12)
Added toxicity	Myelotoxicity Neurotoxicity	Myelotoxicity	Hand and foot Mucositis	Myelotoxicity LFTs

Generally Accepted Guideline for Chemotherapy at Recurrence



Merci !