Recurrent Ovarian Cancer

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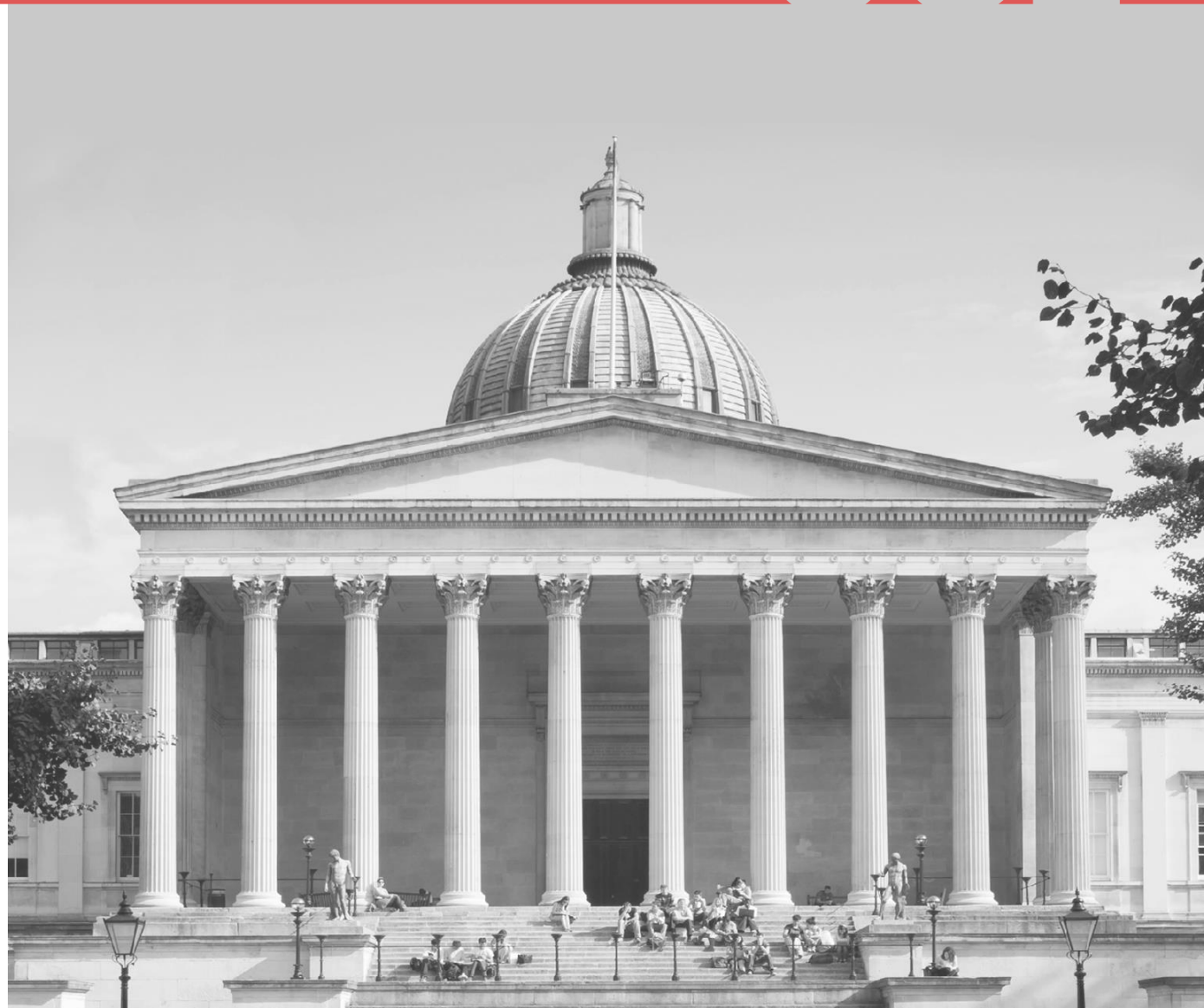
ESMO Preceptorship, Prague, April 2017



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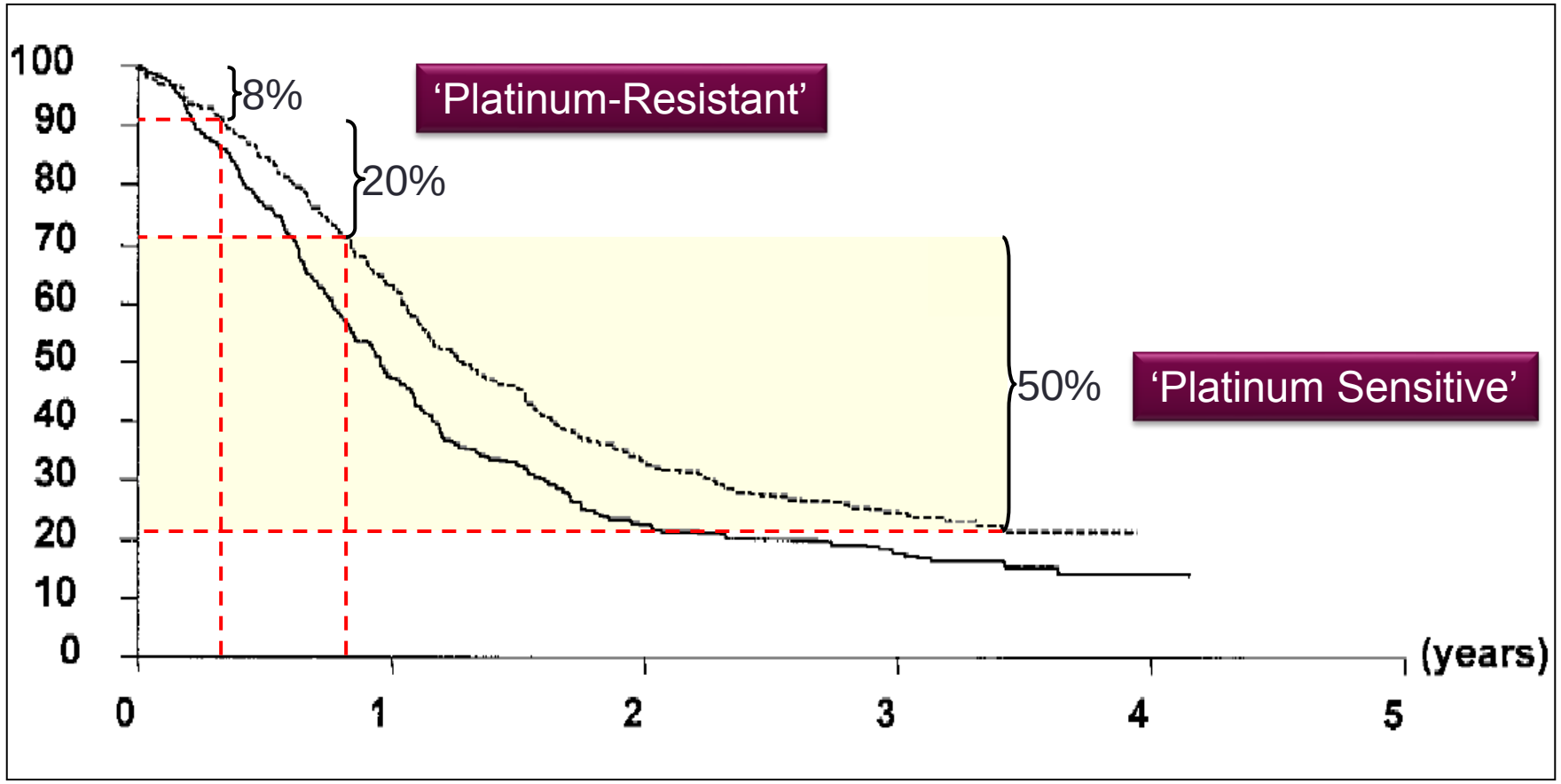
Second-line therapy of Ovarian Cancer



~75% patients with advanced ovarian cancer develop recurrent or progressive disease

Modified from Piccart *et al,* JNCI. 2000; 92: 699–708.

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Recurrent Ovarian Cancer

- When to treat?
- What are the decision points ?
- What to treat with?
- How long to treat?
- How to evaluate treatment?

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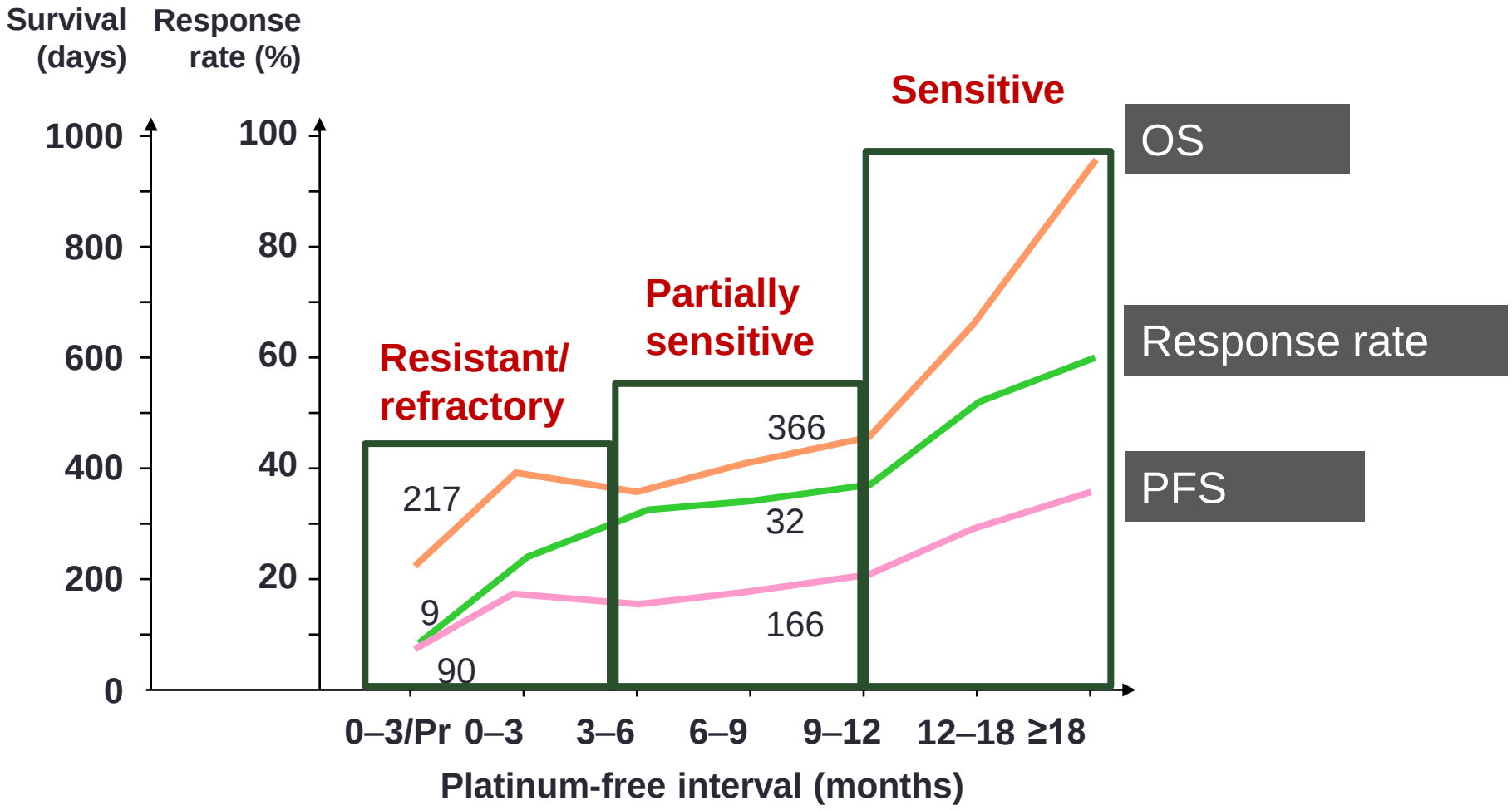
Platinum-free interval and efficacy



Pujade-Lauraine E, *et al. J Clin Oncol* 2002;21(May 20 Suppl):Abstract 829 and presentation

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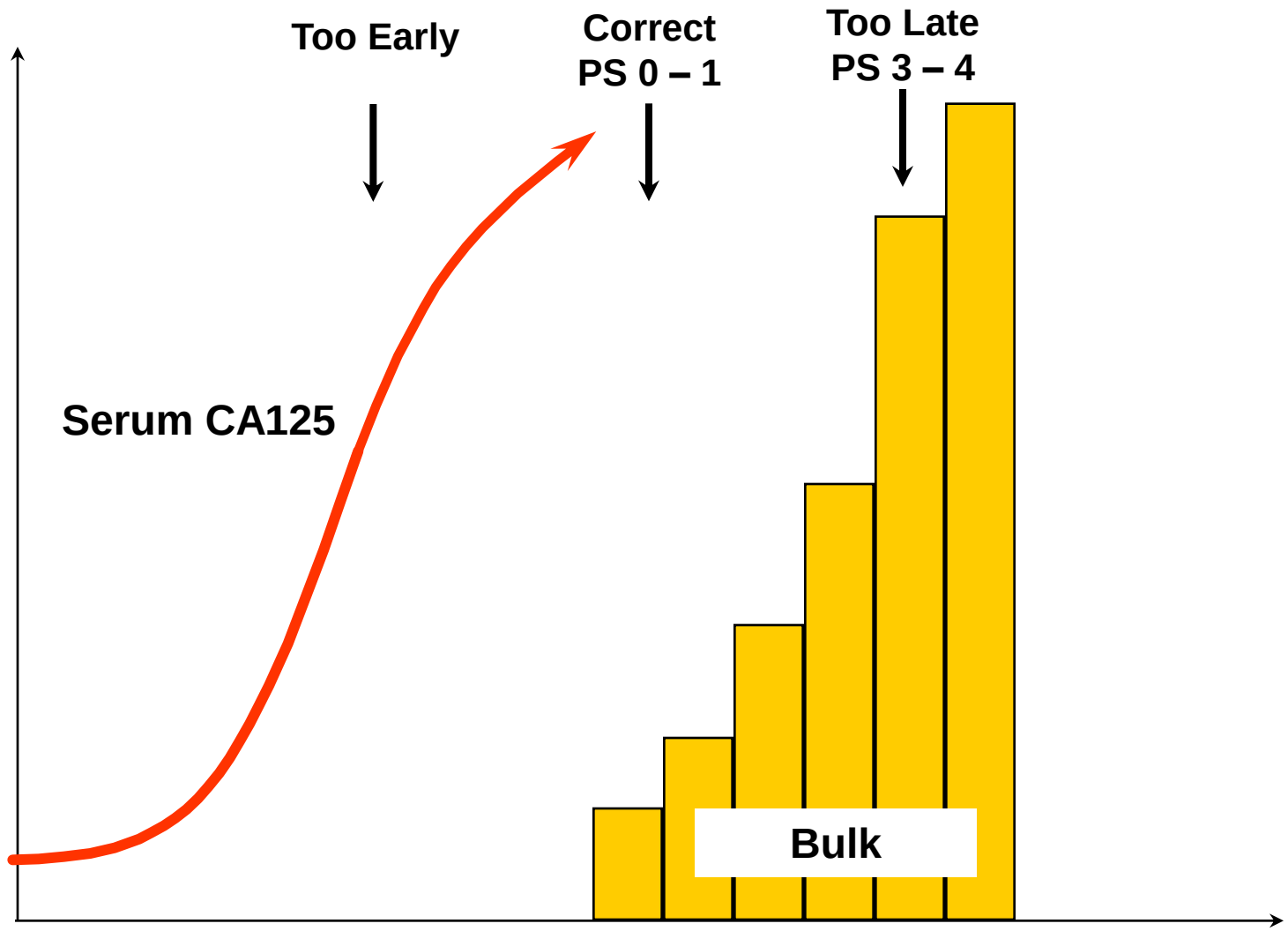
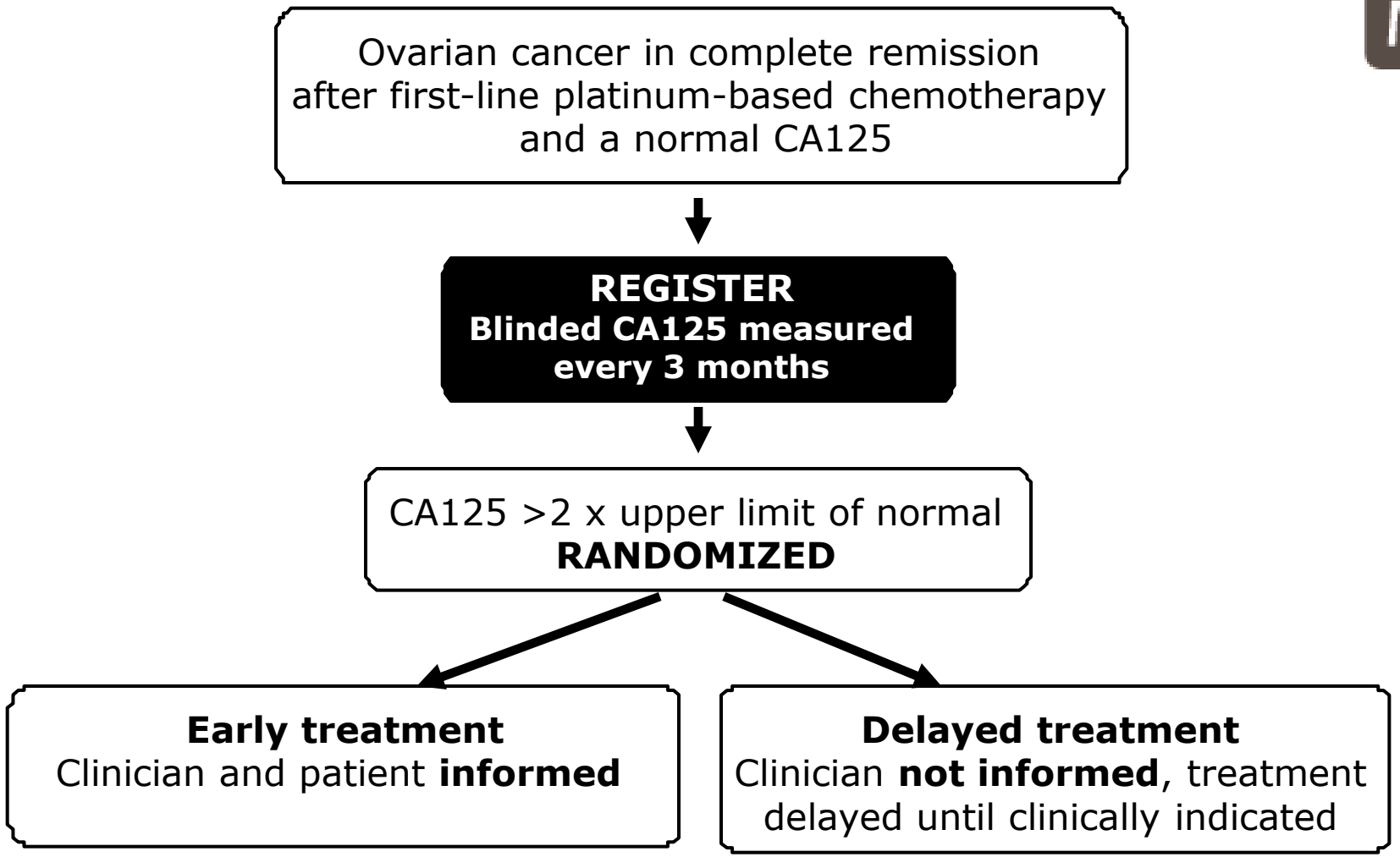
OVARIAN CANCER Treating relapse



Gore 2001, *ASCO Education Book*

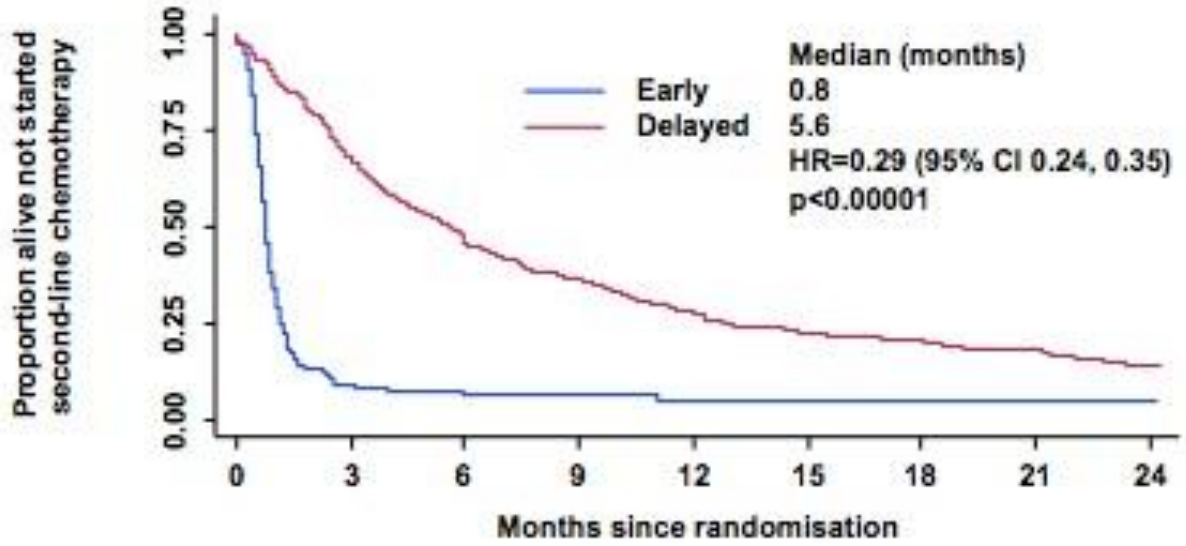
MRC OV 05/ EORTC 55959



Rustin G, et al Lancet 2010; 376: 1155 (2010)

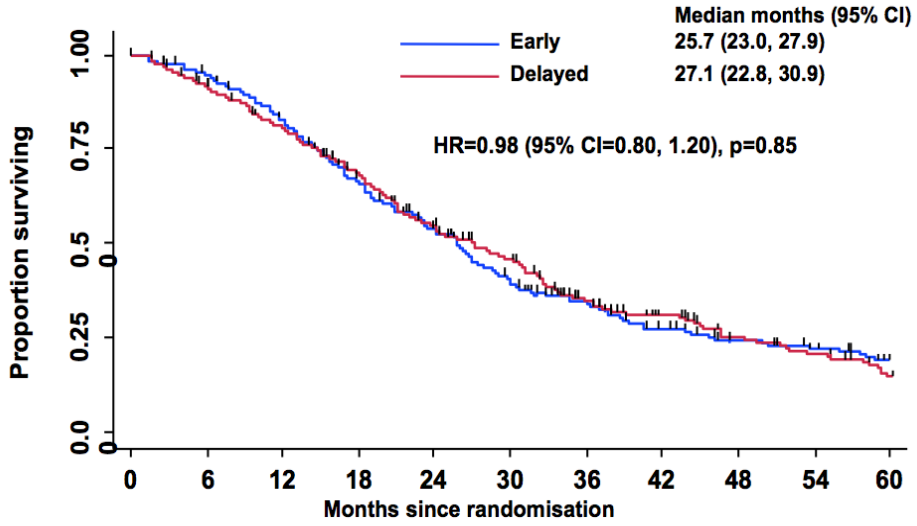
MRC OV 05/EORTC 55959

Time from randomisation 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	

Overall Survival



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

Rustin G et al., Lancet 2010; 376: 1155

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Does surgical cytoreduction improve survival of patients with 'platinum-sensitive' recurrence?

AGO-OVAR DESKTOP III (Protocol AGO - OVAR OP.4- GCIG study)

Surgery - Randomisation

↓

Platinum-based chemotherapy

+ve AGO score

- ECOG PS = 0
- Complete initial debulking
- <500ml ascites

GOG 213

Surgery - Randomisation

↓

Carboplatin/paclitaxel +/- bevacizumab

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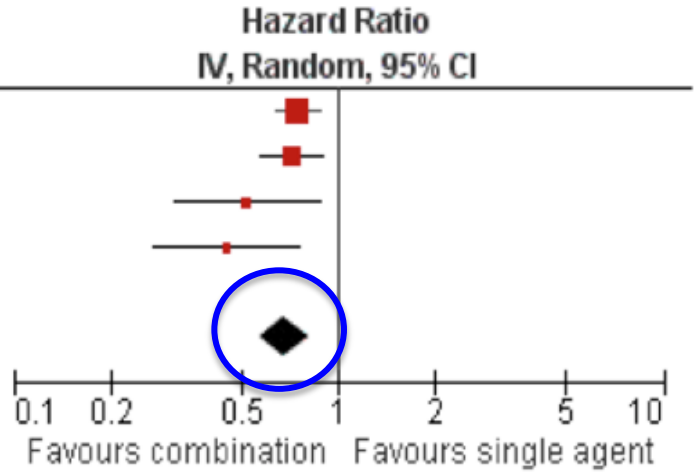
Meta-analysis of combination chemotherapy trials in platinum-sensitive relapsed ovarian cancer

Progression-freel survival

Study	Weight	Hazard Ratio IV, Random, 95% CI
ICON & AGO 2003	46.9%	0.75 [0.65, 0.87]
Pfisterer et al 2006	33.7%	0.72 [0.58, 0.90]
Alberts et al 2007	9.6%	0.52 [0.31, 0.88]
González-Mart. et al 2005	9.8%	0.45 [0.27, 0.76]
Total (95% CI)	**100.0%**	**0.68 [0.57, 0.81]**

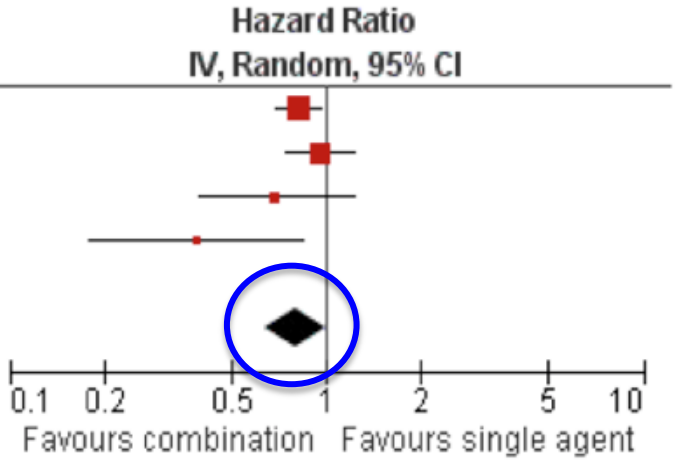
Heterogeneity: Tau² = 0.01; Chi² = 4.70, df = 3 (P = 0.19); I² = 36%
Test for overall effect: Z = 4.30 (P < 0.0001)



Overall survival

Study	Weight	Hazard Ratio IV, Random, 95% CI
ICON & AGO 2003	44.8%	0.81 [0.69, 0.97]
Pfisterer et al 2006	35.1%	0.96 [0.75, 1.23]
Alberts et al 2007	12.7%	0.69 [0.39, 1.21]
González-Mart. et al 2005	7.5%	0.39 [0.18, 0.84]
Total (95% CI)	**100.0%**	**0.80 [0.64, 1.00]**

Heterogeneity: Tau² = 0.02; Chi² = 5.44, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 1.96 (P = 0.05)



Raja et al Ann Oncol 2013

Platinum combinations

	Advantages	Disadvantages
Carboplatin/ Paclitaxel	• Survival advantage [ICON4]	• Compounding toxicity seen in first line; • Less able to use weekly paclitaxel at 'platinum-resistant' relapse

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Partially sensitive platinum-ovarian cancer : Is non-platinum-based treatment an option?

Phase III studies in patients who recur within 6–12 months

Treatment	Group/Name	Median PFS, months
Carboplatin-PLD[1]	CALYPSO	9.4
Carboplatin-paclitaxel[1]	CALYPSO	8.8
Carboplatin-gemcitabine	AGO-GCIG	7.9
Trabectedin-PLD[2]	OVA-301	7.4
PLD[2]	OVA-301	5.5
Carboplatin	AGO-GCIG	5.2

1. Pujade-Lauraine PE, et al. *J Clin Oncol* 2010;28:3323–3329
2. Poveda A, et al. *Ann Oncol* 2010;

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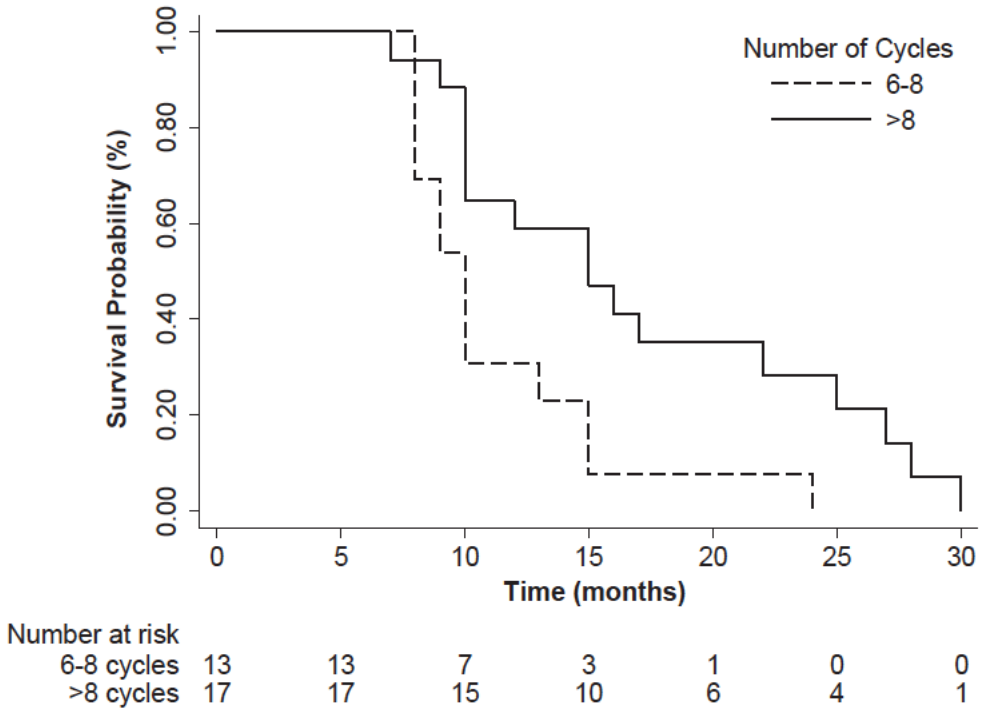
How long to treat?

Kaplan-Meier Progression-Free Survival

PLD 6-8 cylces versus > 8 cycles



Characteristic	Cycles 6-8 (n = 13)	Cycles >8 (n = 17)	P
Mean Age, Years	62	55	.08
Stage			1.0
1 or 2	0	1	
3 or 4	12	15	
Unknown	1	1	
Optimal Resection	10	10	.4
Tumor Type			.7
Ovary	12	15	
Primary Peritoneal	0	2	
Other	0	1	
Platinum-Sensitive	9	10	.7
Line of Treatment			.2
Second	6	10	
Third	7	4	
Fourth or greater	0	3	

Cronin etal. Clinical Ovarian and Other Gynecologic Cancer: 2014

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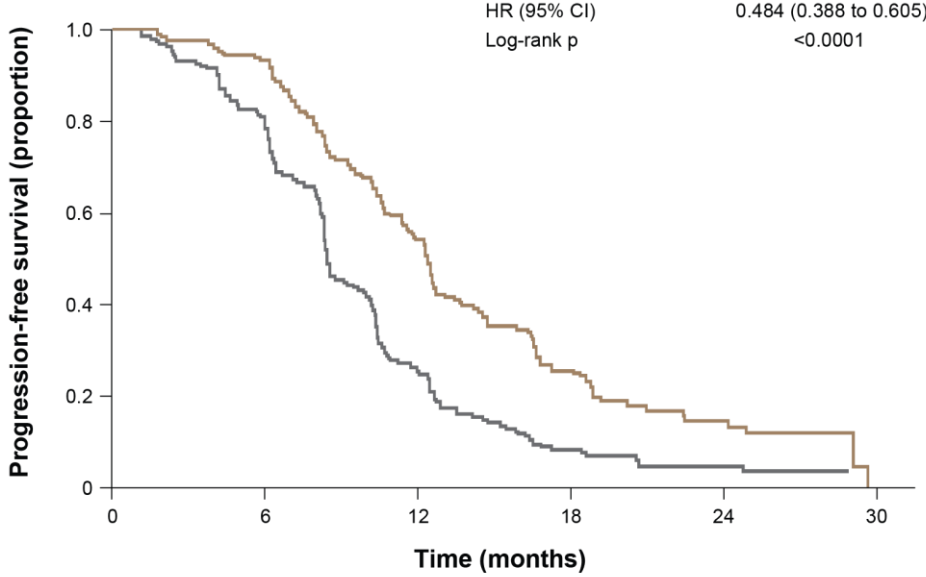
Anti-angiogenic therapy

OCEANS: first platinum-sensitive relapse

carboplatin/gemcitabine +/- bevacizumab

Progression-free survival

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

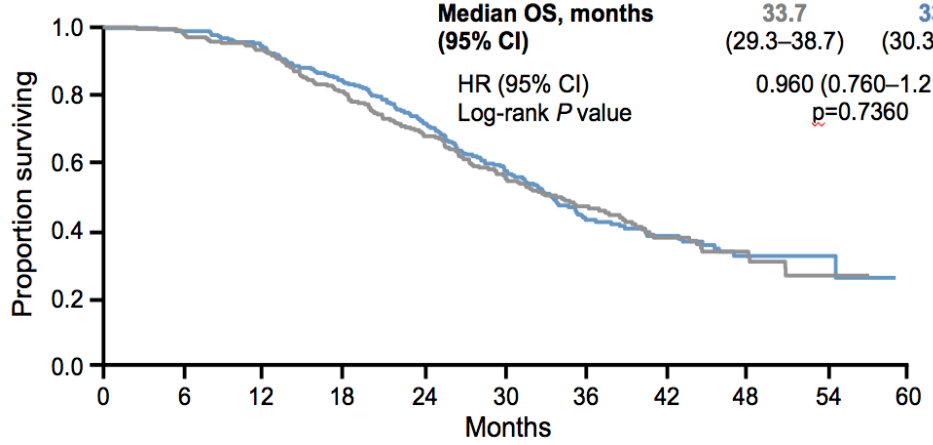


No. at risk						
GC + PL	242	177	45	11	3	0
GC + BV	242	203	92	33	11	0

Aghajanian C, et al. J Clin Oncol 2012;30:2039–45

Third interim overall survival analysis

	GC + PL (n=242)	GC + BV (n=242)
Events, n (%)	142 (58.7)	144 (59.5)
Median OS, months (95% CI)	33.7 (29.3–38.7)	33.4 (30.3–35.8)
HR (95% CI)	0.960 (0.760–1.214)	
Log-rank *P* value	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, Goff et al ESMO 2012

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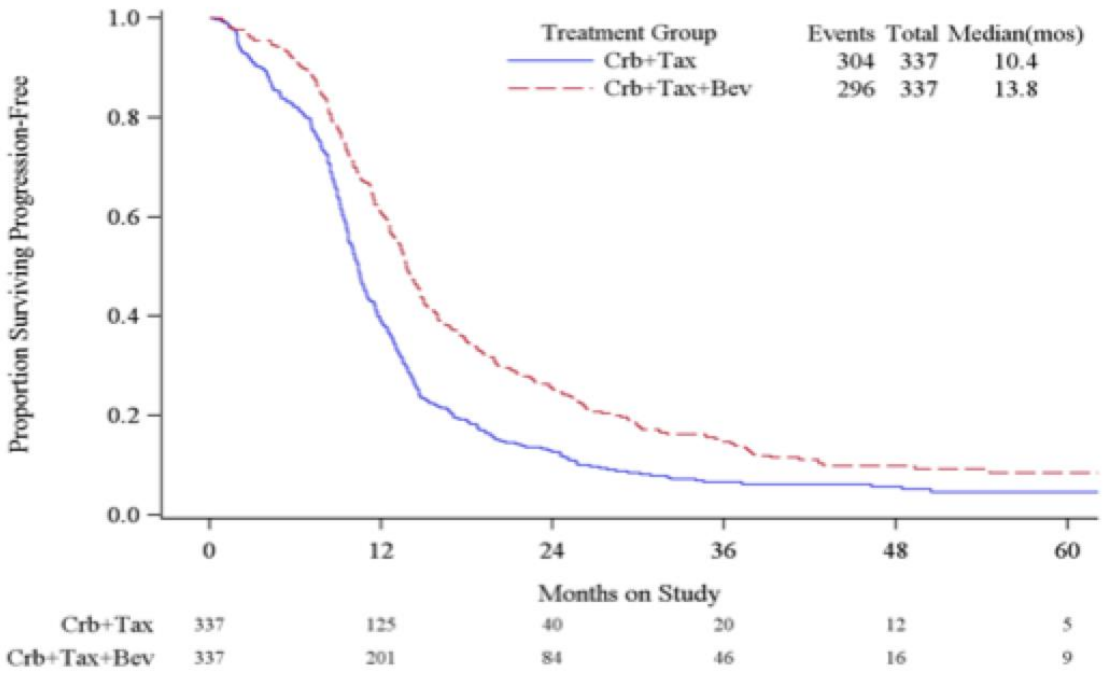
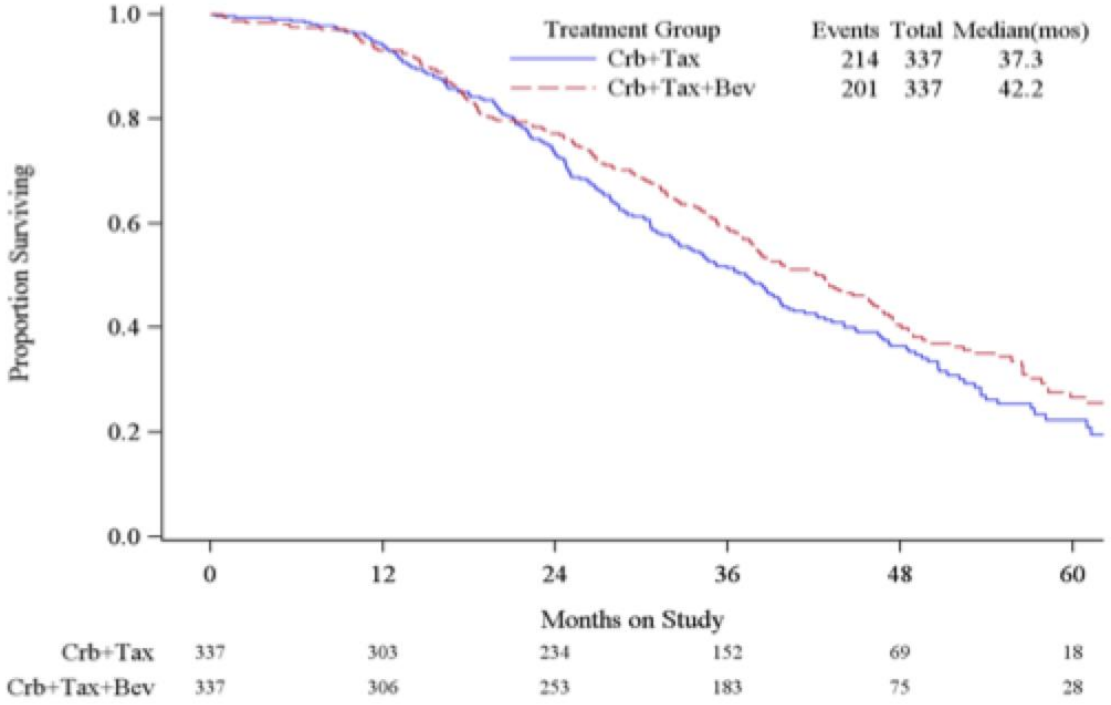
GOG 213 outcome

Progression-Free survival



HR_{adj}:0.61 (0.52 – 0.72), P <0.0001

Overall survival



HR_{adj}:0.829 (0.683 – 1.005), P=0.056

Coleman, R et al SGO Chicago 2015

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Anti-angiogenic agents in recurrent ovarian cancer

	Platinum Sensitive			Platinum-resistant (< 6 month PFI) and Partially Platinum-sensitive equally divided	Platinum-Resistant	
	OCEANS (n= 484)	**GOG213 (n=674)**	**ICON6 N= 456)**	**TRINOVA-1***	**AURELIA* (n= 361)**	**MITO11* (n=74)**
	Carboplatin/ gemcitabine ± **bevacizumab**	Carboplatin/ paclitaxel ± **bevacizumab**	Platinum-based ± **cediranib**	Weekly paclitaxel ± **trebananib**	weekly paclitaxel, PLD, topotecan ± **bevacizumab**	Weekly paclitaxel ± **pazopanib**
PFS (med. months)	**8.4 v 12.4**	**10.4 v 13.8**	**8.7 v 11.1**	**7.2 v 5.4**	**3.4 v 6.7**	**3.5 v 6.4**
HR	**0.484** (p<0.0001)	**0.61** (p<0.0001)	**0.57** (p=0.00001)	**0.66** (p < 0.0001)	**0.48** (p<0.001)	**0.42** (p=0.0002)

Pazopanib and Cediranib: Oral VEGF receptor tyrosine kinase inhibitors
Trebananib (AMG386): Peptibody inhibiting angiopoeitin 2

* Non maintenance therapy

(OCEANS) Aghajanian et al JCO 2011; (GOG 213) Coleman et al SGO 2015; (ICON6) Ledermann et al ECC (2013);
(TRINOVA-1) Monk et al Lancet Oncol 2014; (AURELIA) Pujade-Lauraine et al JCO 2014;
(MITO11) Pignata et al Lancet Oncol 2015

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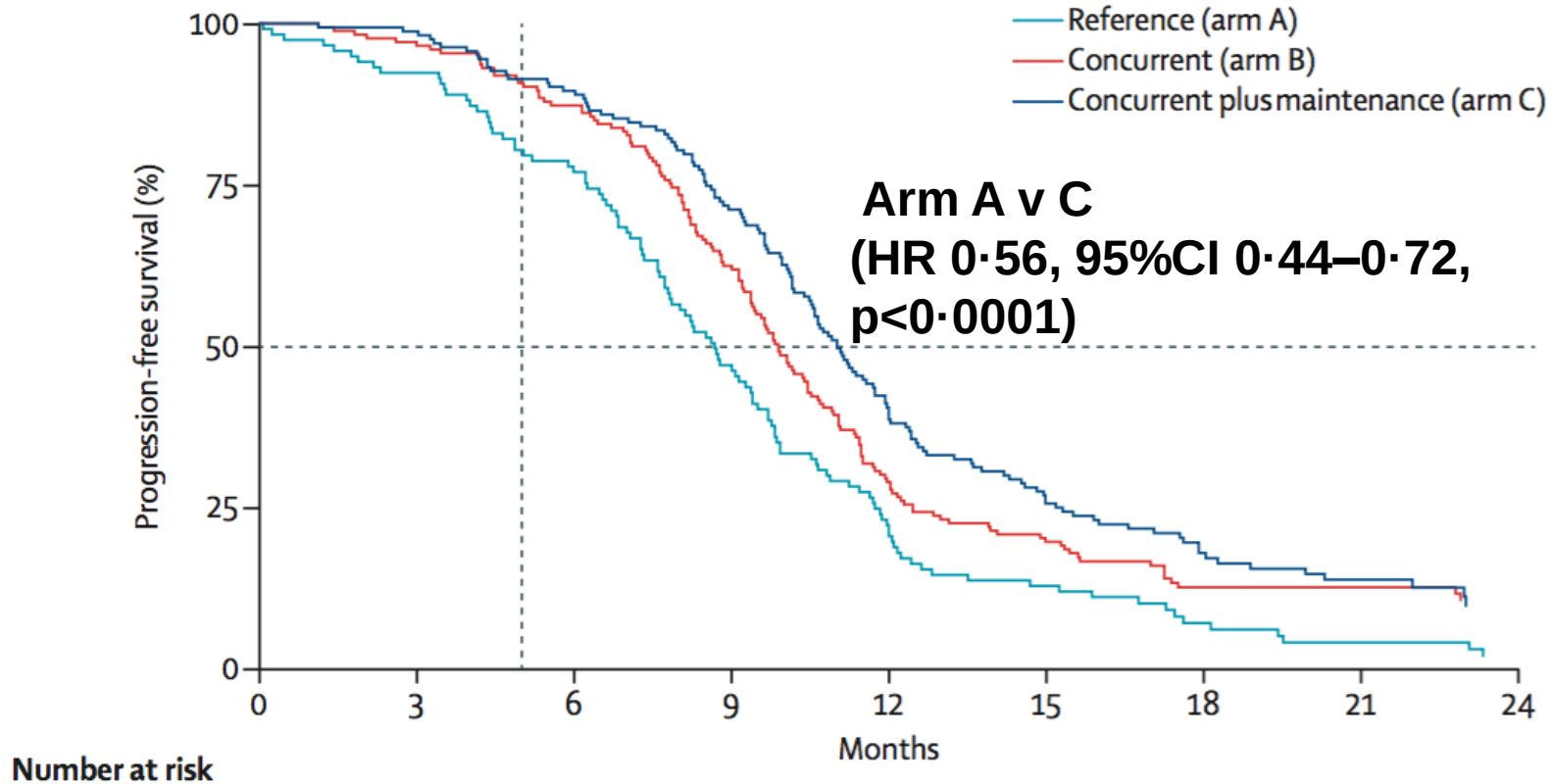
ICON 6: cediranib in recurrent ovarian cancer Progression-Free Survival

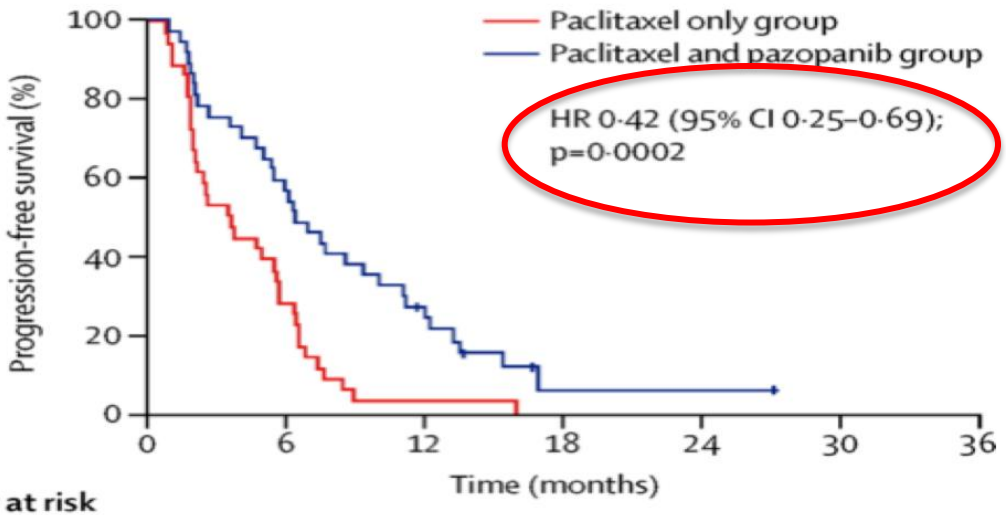


Number at risk (events)									
Arm A	118	(27)	90	(66)	24	(15)	7	(5)	2
Arm B	174	(22)	151	(100)	51	(28)	18	(2)	11
Arm C	164	(17)	146	(83)	63	(32)	22	(8)	7

Ledermann et al Lancet 387: 1066-74 2016

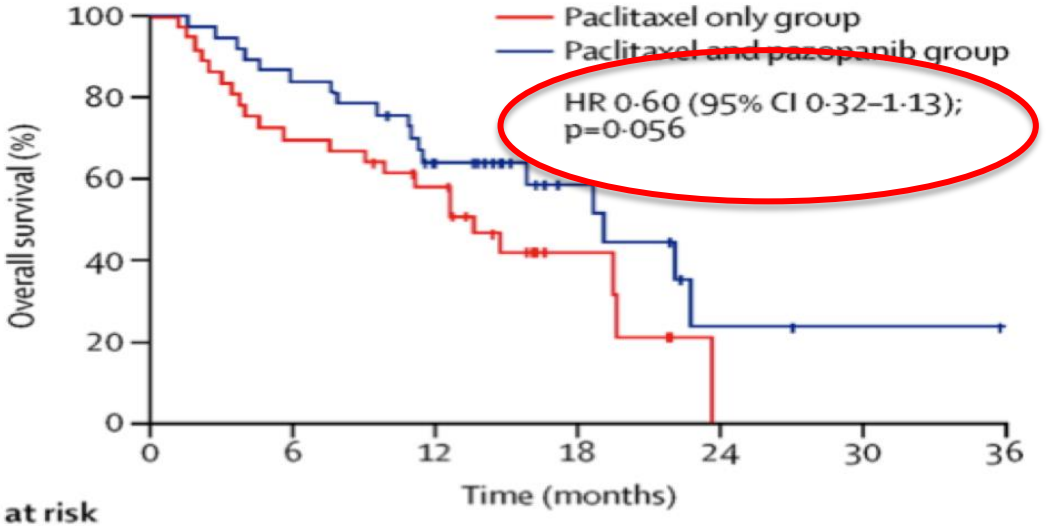
MITO11 Paclitaxel and Pazopanib in platinum-resistant ovarian cancer

Progression-free Survival



Number at risk					
Paclitaxel only group	36	11	2	0	0
Paclitaxel and pazopanib group	37	22	10	2	2

Overall Survival



Number at risk							
Paclitaxel only group	36	26	19	5	0	0	0
Paclitaxel and pazopanib group	37	32	21	9	3	2	1

Pignata et al Lancet Oncol 2015

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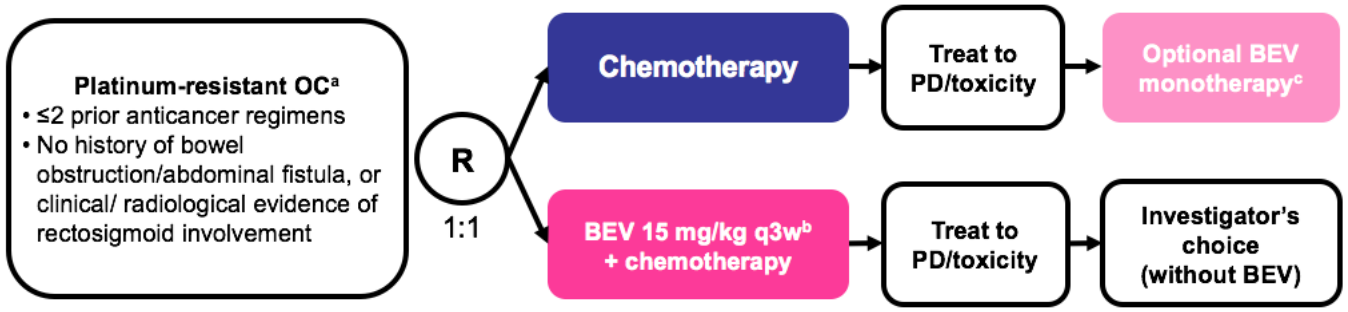
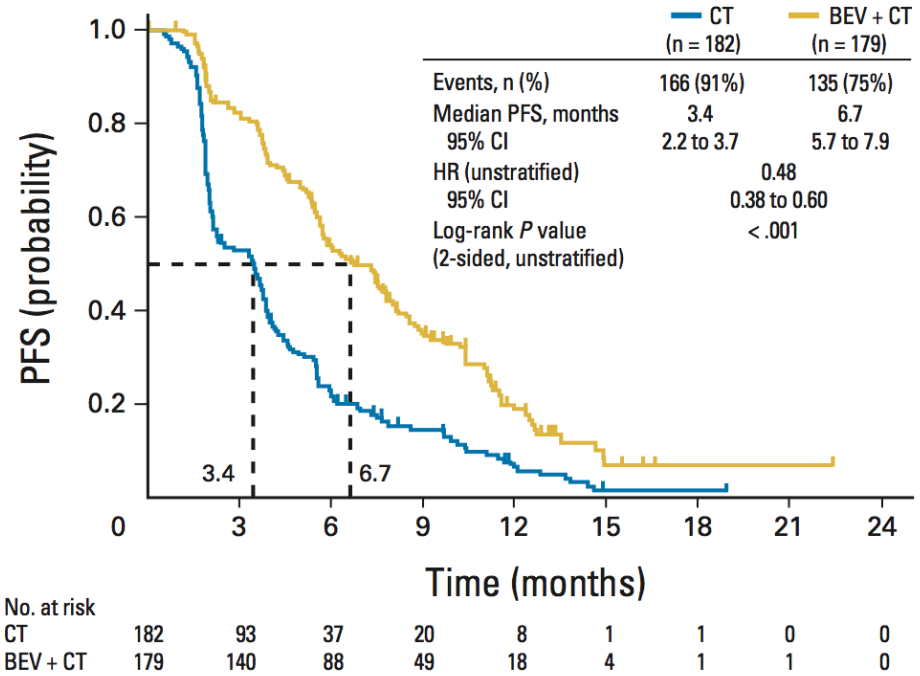
AURELIA: bevacizumab in 'platinum-resistant' ovarian cancer

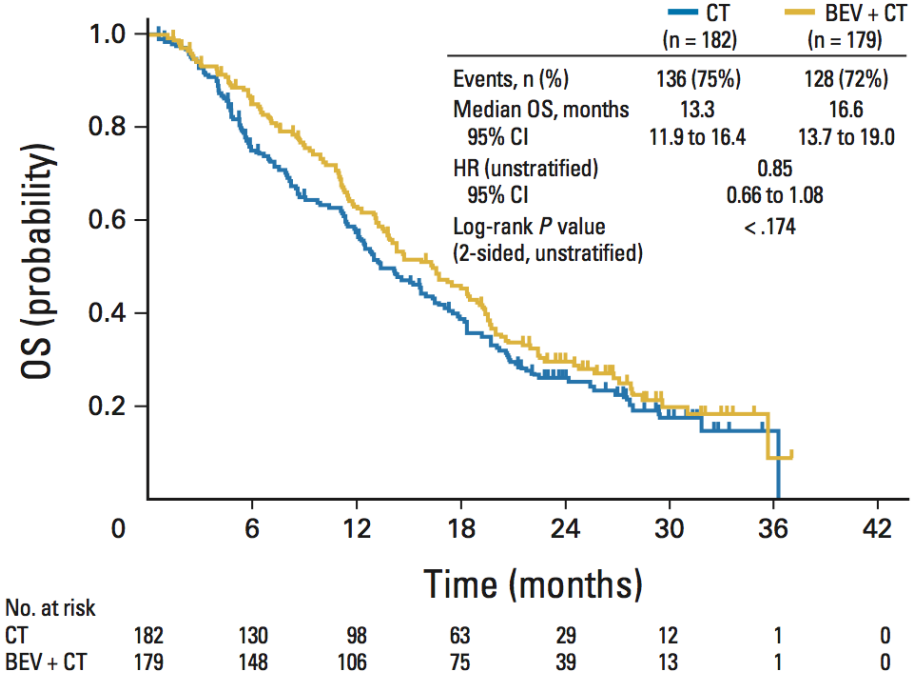


- Weekly paclitaxel
- PLD
- Topotecan

PFS



OS



Pujade-Lauraine et al J Clin Oncol 32:1302-8(2014)

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Maintenance Strategies

- PARP inhibitors post-platinum therapy
  - Olaparib in BRCA mutated high grade serous platinum-senstive cancer (germline and somatic)
  - Niraparib in all patients with platinum-sensitive ovarian cancer after response to platinum-based therapy (FDA)

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5th Ovarian Cancer Consensus Meeting – Tokyo, November 2015

D1. What are the subgroups for clinical trials in recurrent ovarian cancer?

1. **Trials in recurrent ovarian cancer should incorporate the following to define the trial population:**
   - Treatment-free interval (TFI)
     - TFIp (platinum)
     - TFInp (non-platinum), TFIb (biological agent to be specified)
   - Histological type
   - BRCA status (gBRCA, and others including somatic BRCA and HRD to be considered as data emerges)
   - Type of prior therapy (anti-angiogenic agents, PARP inhibitors, chemotherapy, and others)
   - Number of prior lines of chemotherapy (trials should not be limited to second or third line)
   - Presence or absence of symptoms and type (e.g. ascites, abdominal symptoms, pain, performance status)

   Other factors to be considered: tumor volume, and previous surgical outcome
2. **Separate trials are needed for populations with unmet needs:**
   - Medically compromised and/or elderly patients
   - Multiple lines of prior chemotherapy

Ann Oncol 2017

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Platinum-resistant / refractory group

Different Biology!

- **Persistent disease: little or no response to first-line therapy**
- **Good partial or complete response and early relapse**
- **Previous multiple lines of treatment**

- ❑ Asymptomatic disease
- ❑ Disease likely to cause organ dysfunction
- ❑ Symptomatic progression or relapse

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Platinum-Resistant Ovarian Cancer

- No evidence that combination therapy is superior to single-agent
- Results of single agent therapy broadly similar
  - Response rates < 20% (in some series less than 10%)
  - Median Progression-Free survival around 3-4 months (chemotherapy courses 3-6 months)
  - Remember platinum!- probably the most active chemotherapy drug in platinum-resistant ovarian cancer!
- Is chemotherapy the right way forward?
  - Bevacizumab RR ~ 16 %
  - Tamoxifen/ letrozole similar RR to chemotherapy
  - Novel (molecular) therapies/clinical trials
- How to evaluate response?

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Response to platinum after an interval of less than 6 months

Treatment Free interval	Cisplatin/Paclitaxel (*de Jong et al. 2002*)	Cisplatin/Etoposide (*van der Burg et al. 2002*)
<4 months	5/8 (63%)	13/28 (46%)
4-12 months	4/7 (57%)	29/32 (91%)
Carboplatin and gemcitabine < 6 month *(Ledermann et al 2010)*		
29% Response rate; 63% CA125 GCIG response rate (n=40)		

Time to reconsider ‘platinum-resistance’ !

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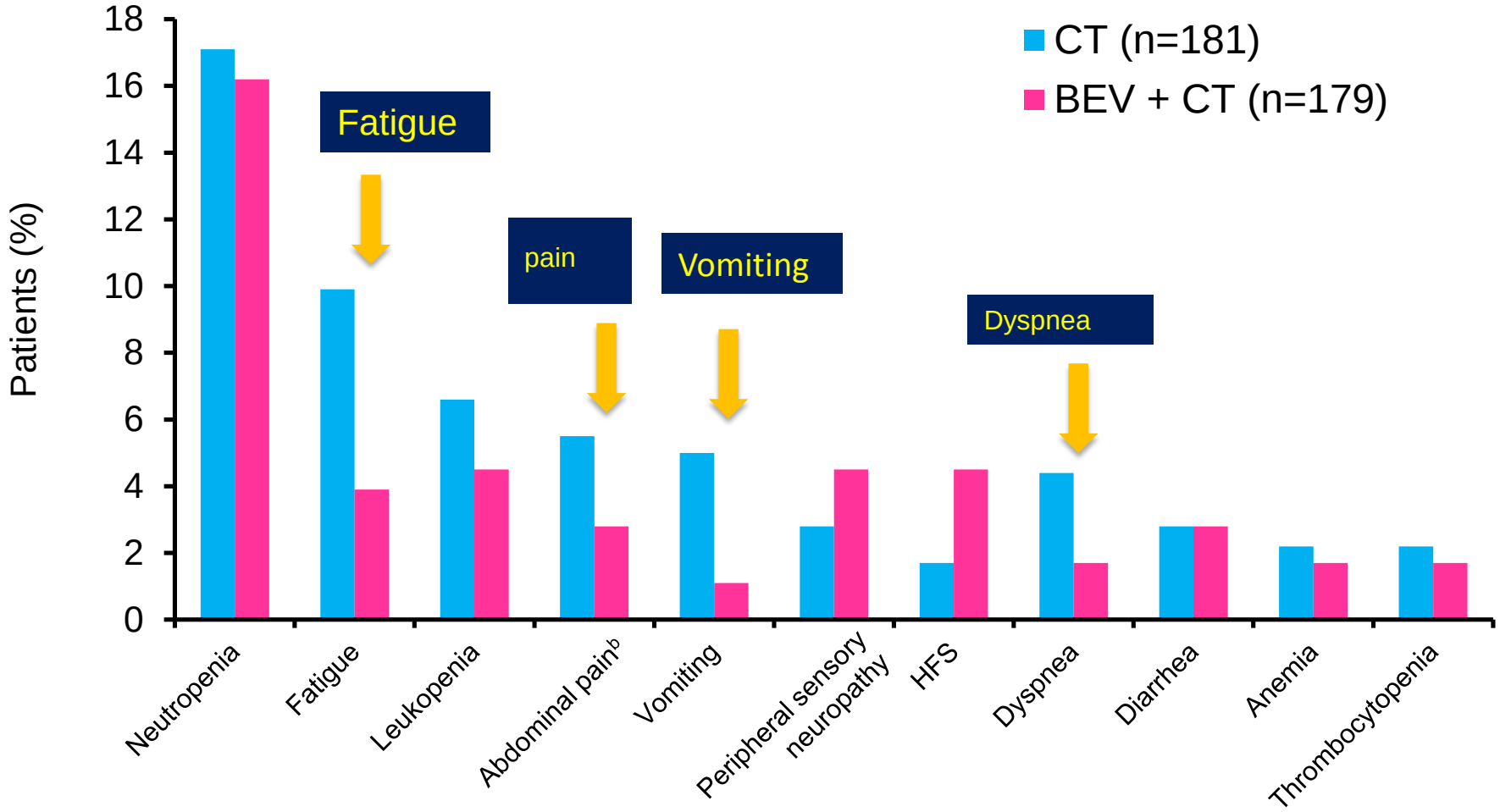
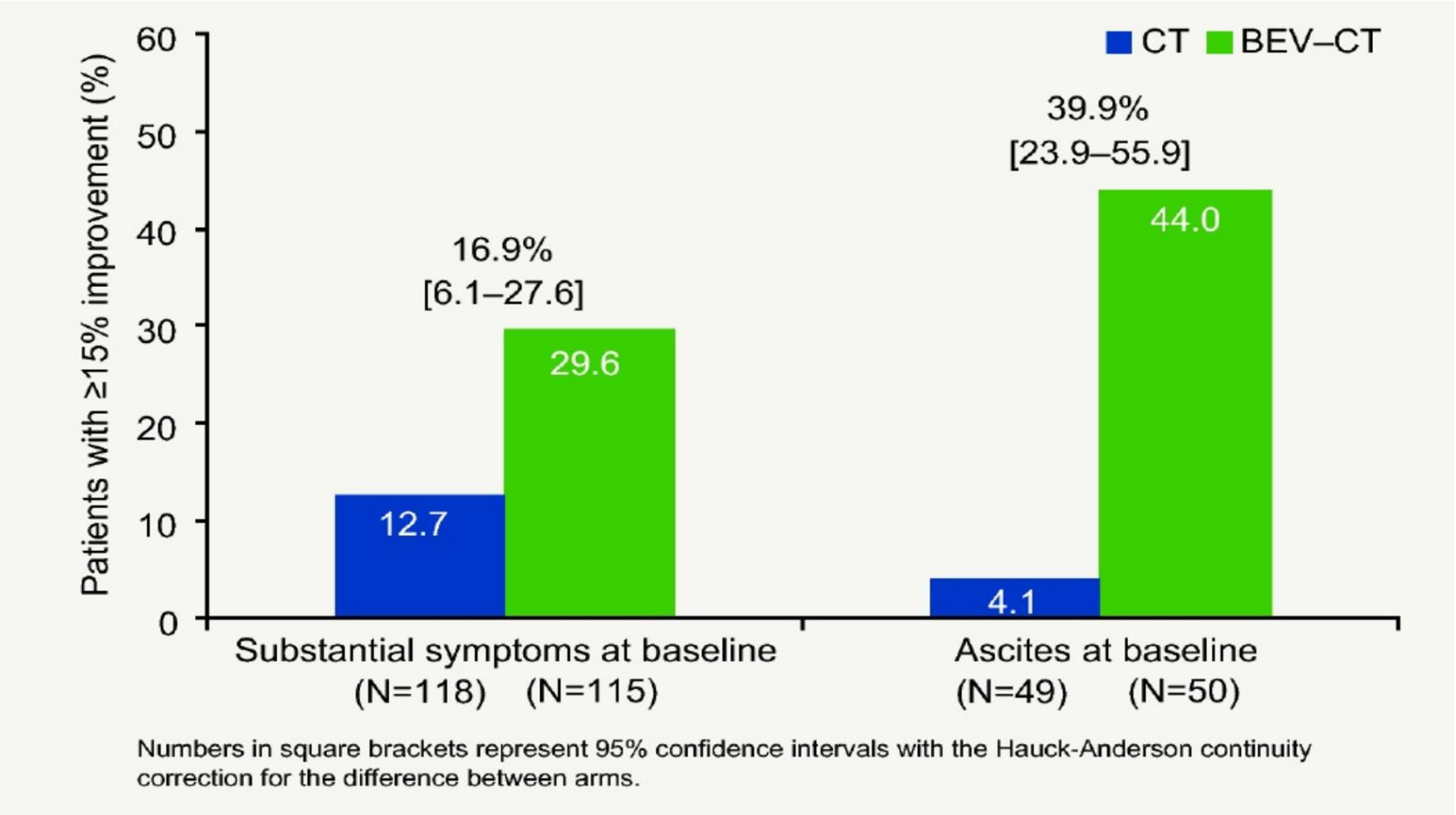
Symptom evaluation in AURELIA Trial



Pujade-lauraine E, ASCO 2012

Aurelia Trial: Health-related QoL

Primary PRO hypothesis (Abdominal/ Gastrointestinal symptoms):
Subgroup analysis week 8/9



Stockler et al ASCO 2013
and J Clin Oncol 32:1309-1 6(2014)

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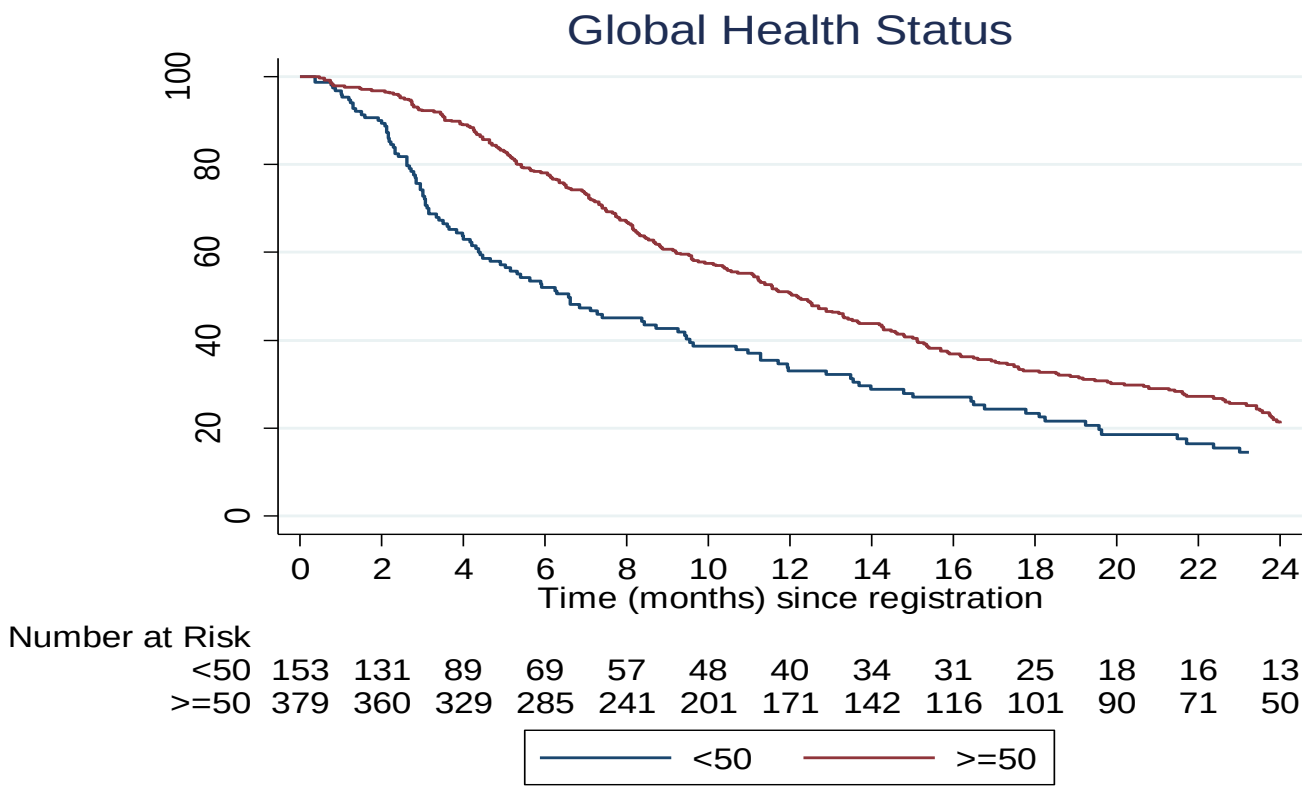
Evaluation of Benefit

- Need to define who should be treated
  - Matching biology to treatment
  - Better evaluation (and use of) prognostic factors for outcome
- What endpoints
  - Response rate/ progression-free survival are poor surrogates for platinum-resistant disease
  - Clinical evaluation scales

Symptoms and evaluation of outcome

Clinical characteristics predictive of overall survival
Mulitvariate analysis

CHARACTERISTIC	HR (95%CI)	p-value
Haemoglobin (per 10g/L increase)	0.94 (0.89 to 0.99)	0.02
Ascites	1.60 (1.27 to 2.01)	<0.0001
Abdominal/GI symptoms (present)	1.24 (1.01 to 1.52)	0.04
Platelets (per 100 x10^9unit increase)	1.10 (1.01 to 1.20)	0.03
Log CA125 (per unit increase)	1.18 (1.11 to 1.27)	<0.0001
Neutrophil : lymphocyte ratio (5 or more)	1.79 (1.41 to 2.28)	<0.0001



Roncolato et al ASCO 2016

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MOST -Developed by GCIG Symptom Benefit Group- Undergoing validation

Measure of Ovarian Cancer Symptoms & Treatment Concerns – Recent

Patient initials: ☐☐☐ (First middle last) Study # ☐☐☐☐☐☐☐ Today's date: ☐☐ (D D) ☐☐ (M M) ☐☐ (Y Y)

Please **circle** one number for each line to best show **how much that aspect troubled you on average during the last 3-4 weeks.**

		No trouble at all		Mild		Moderate			Severe			Worst I can imagine
1.	Pain (all and anywhere)	0	1	2	3	4	5	6	7	8	9	10
2.	Fatigue (tiredness)	0	1	2	3	4	5	6	7	8	9	10
3.	Poor appetite (or feeling full quickly)	0	1	2	3	4	5	6	7	8	9	10
4.	Abdominal pain, discomfort and/or cramps	0	1	2	3	4	5	6	7	8	9	10
5.	Abdominal swelling, bloating and/or fullness	0	1	2	3	4	5	6	7	8	9	10
6.	Trouble eating	0	1	2	3	4	5	6	7	8	9	10
7.	Indigestion	0	1	2	3	4	5	6	7	8	9	10
8.	Nausea	0	1	2	3	4	5	6	7	8	9	10
9.	Vomiting	0	1	2	3	4	5	6	7	8	9	10
10.	Diarrhoea	0	1	2	3	4	5	6	7	8	9	10
11.	Constipation	0	1	2	3	4	5	6	7	8	9	10
12.	Bladder problems	0	1	2	3	4	5	6	7	8	9	10
13.	Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
14.	Leg swelling	0	1	2	3	4	5	6	7	8	9	10
15.	Trouble sleeping	0	1	2	3	4	5	6	7	8	9	10

Please circle one number for each line to show how you would have rated yourself on that aspect on average **during the last 3-4 weeks.**

		Best possible		Very Good		Good		Fair		Poor		Very poor	Worst possible
16.	Physical well-being	10	9	8	7	6	5	4	3	2	1		0
17.	Emotional well-being	10	9	8	7	6	5	4	3	2	1		0
18.	Overall well-being	10	9	8	7	6	5	4	3	2	1		0

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

Summary

- **Treatment of recurrent ovarian cancer represents a significant clinical challenge**
- Requires an understanding of:
  - Biology
  - Wide variety of treatments
  - Treatments choices at different points in the disease pathway
  - Patient factors- prognostic and predictive of outcome
  - Patient choices
- Number of therapeutic opportunites are increasing- molecular targeting and immunotherapy- making choices harder
- Critical appraisal of endpoints needed
  - Balancing the effect of treatment on disease control
  - Side effects
  - Quality of Life