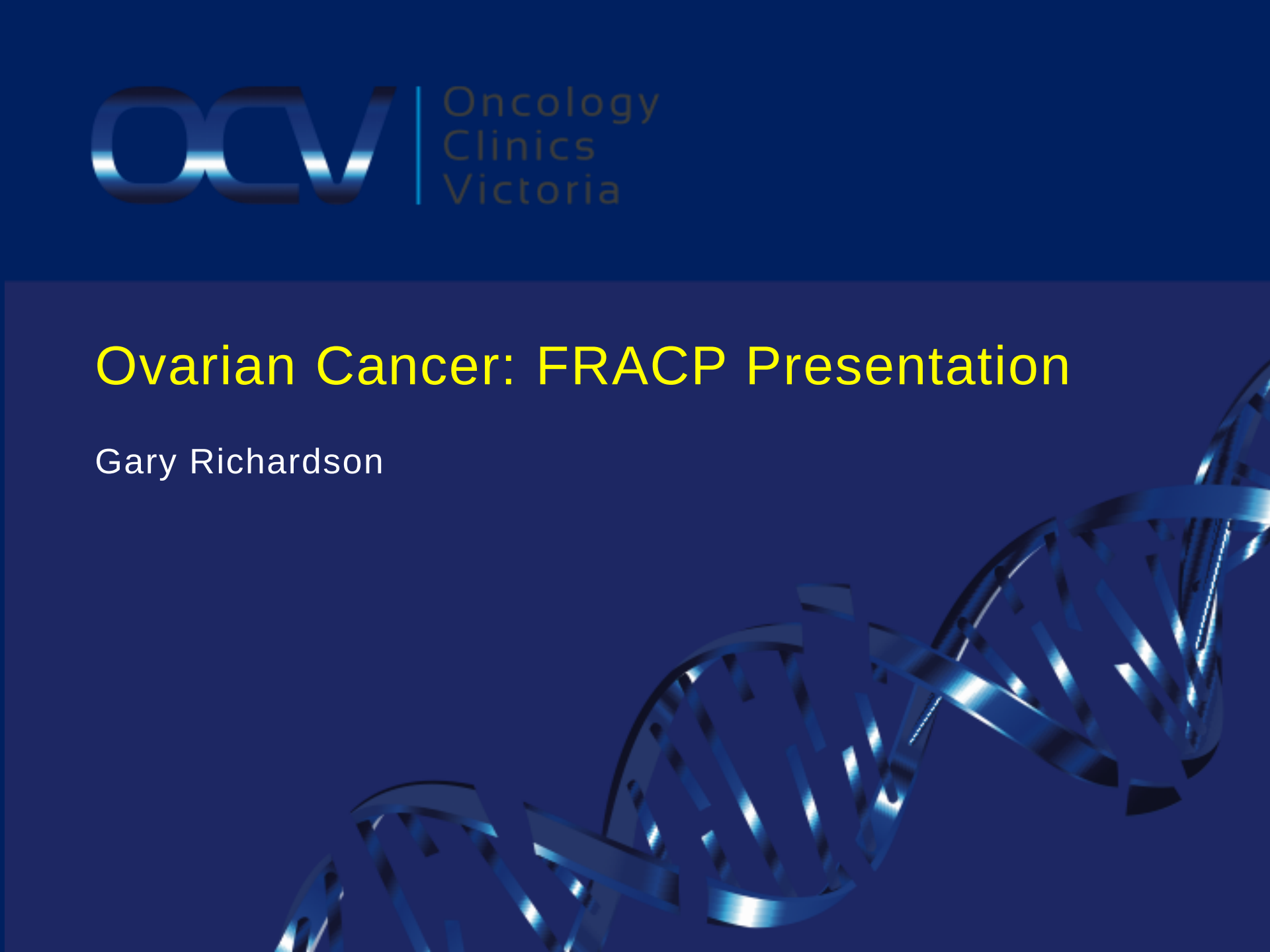
Oncology Clinics Victoria

Ovarian Cancer: FRACP Presentation

Gary Richardson

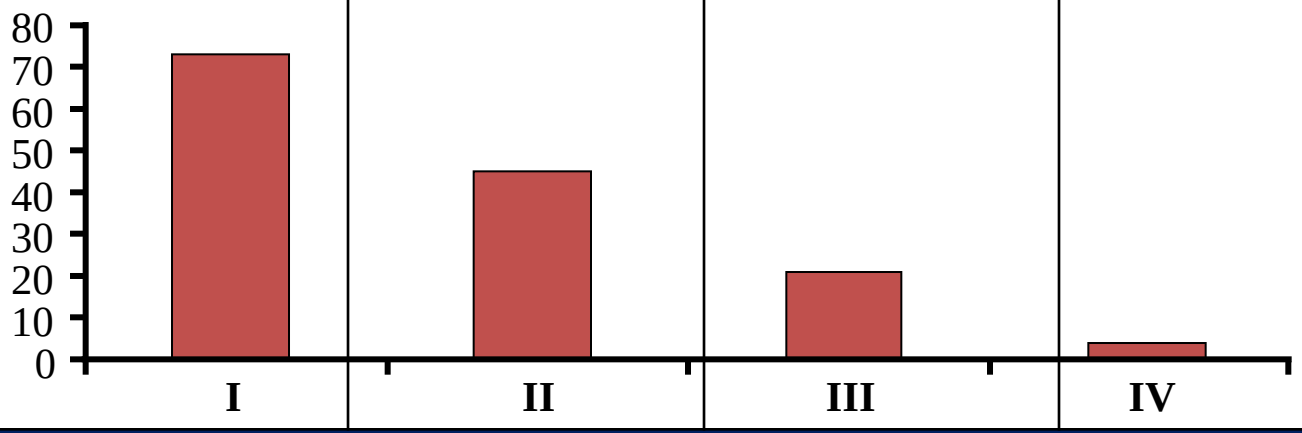


Demographics

- Over 1,600 new cases in 2010
- 4% of all cancer and 5% of all cancer deaths
- One of the most common gynaecological malignancies
- Fifth most frequent cause of cancer death in women
- Median age of diagnosis 63 years
- Since 1970's, little change in incidence & death rates
- Yearly mortality in ovarian cancer is approximately 65% of the incidence rate

Steep Survival Gradient of Ovarian Cancer and Stage at Diagnosis

Stage	I	II	III	IV
Description	Confined to ovaries	Confined to pelvis	Confined to abdomen/lymph nodes	Distant metastases
Incidence	20%	5%	58%	17%
Survival	73%	45%	21%	< 5%



Jelic S, et al. 2002 Congress of the European Society for Medical Oncology. Mocharnuk R. Available at: http://www.medscape.com/viewarticle/444134.

Ovarian Cancer Risk Factors

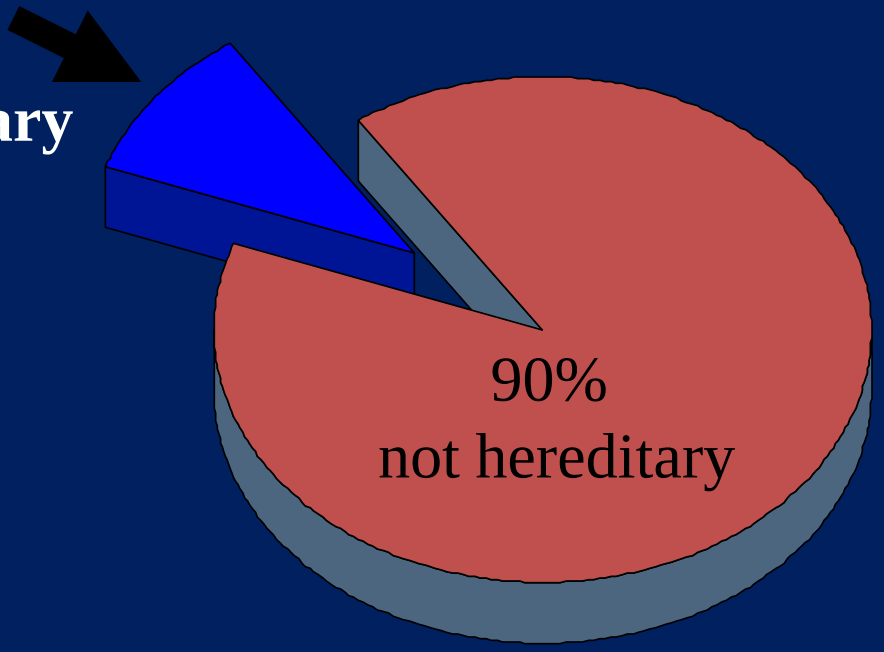
- 50 years of age or older
- Familial factors
  - Family history of breast, ovarian, or colon cancer
  - Personal history of breast or colon cancer
  - BRCA (breast cancer) gene mutation
  - Hereditary nonpolyposis colon cancer (HNPCC)
- Other potential risk factors
  - Early menarche (younger than 12 years of age)
  - Late menopause (older than 52 years of age)
  - Hormone replacement therapy or fertility drugs
  - First pregnancy at older than 30 years of age
  - Infertility

Ovarian Cancer and Early Detection

- Certain factors may reduce a woman's risk of developing ovarian cancer :
  - Taking birth control pills for more than 5 years
  - Breastfeeding
  - Pregnancy
  - A hysterectomy or a tubal ligation

How Much Cancer Is Hereditary?

~5% to 10% of breast, colon, endometrial, and ovarian cancers are hereditary



Cancer Susceptibility Syndromes Involving Gynecologic Cancers

- BRCA: breast and ovarian cancers
- Lynch syndrome (HNPCC): colon and endometrial cancers

Lifetime Risk of Cancers Associated With Specific Genes

Cancer, %	BRCA1	BRCA2	MMR*
Breast	35-60	30-55	0
Ovarian	30-40	15-25	6-20
Endometrial	0	0	40-60

*MMR (mismatch repair) = HNPCC

Chen S, et al. J Clin Oncol. 2007:25:1329-1333.
Aarnio M, et al. Int J Cancer. 1999:81:214-218.

Red Flags for Cancer Susceptibility: BRCA1/BRCA2

- Multiple family members with ovarian or breast cancer
- Age of onset of breast cancer
  - Younger than 50 years of age (premenopausal)
- Bilateral breast cancer
- Both breast and ovarian cancer in same patient
- Ashkenazi Jewish ancestry
- Male breast cancer

Natural History

- Precise natural history is poorly understood
- It has not been established that untreated stage I routinely progresses to more advanced stages
- The entire peritoneum is at risk because peritoneal carcinomatosis may develop after an oophorectomy
- There is no direct evidence for a premalignant lesion in ovarian cancer.

Screening

- Currently available screening techniques (ovarian palpation, trans-vaginal ultrasound, and serum CA-125 determinations) are not sufficiently accurate for general screening.
- Screening for ovarian cancer has not been proven to decrease the death rate from the disease.
- There is no evidence to support the use of any test, or combination of tests currently available, to screen women for ovarian cancer on an individual basis or through a population-based screening approach – NBOCC Position Statement (2011)

Screening

Country	Participants	Stage I	Total
Sweden	5,550	2	6
UK	5,479	5	9
UK	21,959	3	11
US	3,220	2	3
Total	36,208	12	29

What Are the Symptoms of Ovarian Cancer?

- Abdominal or pelvic discomfort or pain
- Persistent indigestion, gas, nausea, diarrhea, or constipation
- Frequent or urgent need to urinate
- Abdominal or pelvic pressure, swelling, or bloating
- Loss of appetite
- Feeling of fullness, even after a light meal
- Unexplained weight loss or gain, especially in the abdominal area
- Abnormal vaginal bleeding
- Pain during sexual intercourse
- Fatigue
- Lower back pain

How is Ovarian Cancer Diagnosed?

- Diagnosis is confirmed with a biopsy
- Pelvic examination
- Transvaginal ultrasound
- CA-125 blood test
- CT scan
- FDG-PET scan
- Cytological examination of ascitic fluid

Ovarian Carcinoma: CA-125

- Serum glycoprotein (OC-125)
- Discovered during a search to boost an immunotherapy (*Corynebacterium parvum*)[1]
- Blood test introduced in 1981
  - Present in 82% ovarian cancers; 1% in controls[2]
- CA-125 cloned in 2001[3]
  - Mapped to chromosome 19 (p13.3)
  - Gene: MUC16
  - Very large molecule

1. Bast RC, et al. J Clin Invest. 1981;68:1331-1337. 2. Bast RC, et al. N Engl J Med. 1983;309:883-887.
3. Yin BW, et al. J Biol Chem. 2001;276:27371-27375.

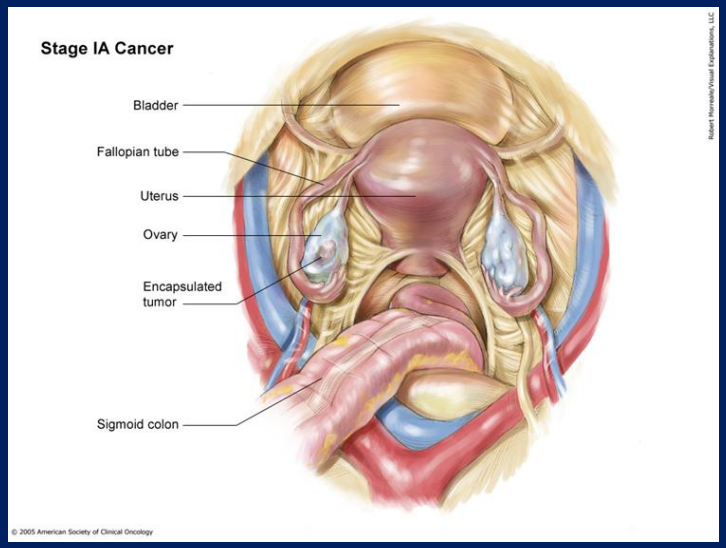
How is Ovarian Cancer Treated?

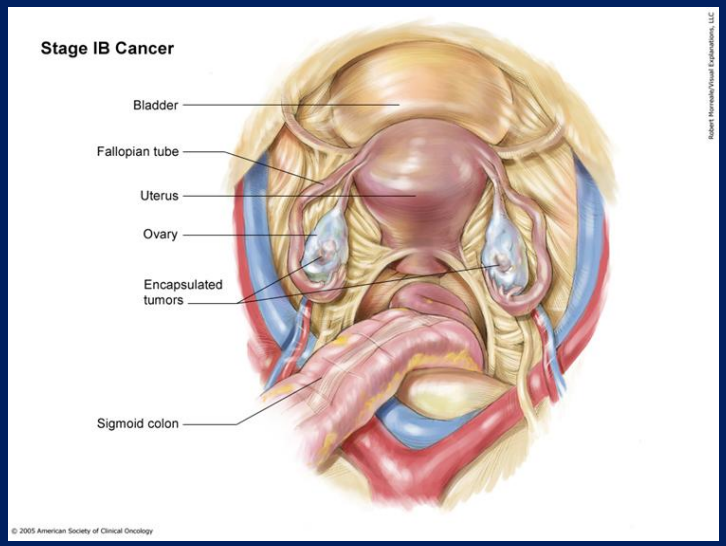
- Treatment depends on stage of cancer
- More than one treatment may be used
- Surgery
- Chemotherapy
- Radiation therapy

Ovarian Cancer Staging

- Staging is a way of describing a cancer, such as the size of the tumor and where it has spread
- Staging is the most important tool doctors have to determine a patient's prognosis
- Staging is described by the TNM system: the size and location of the Tumor, whether cancer has spread to nearby lymph Nodes, and whether the cancer has Metastasized (spread to other areas of the body)
- Some stages are divided into smaller groups that help describe a patient's condition in more detail
- Treatment depends on the stage of the cancer

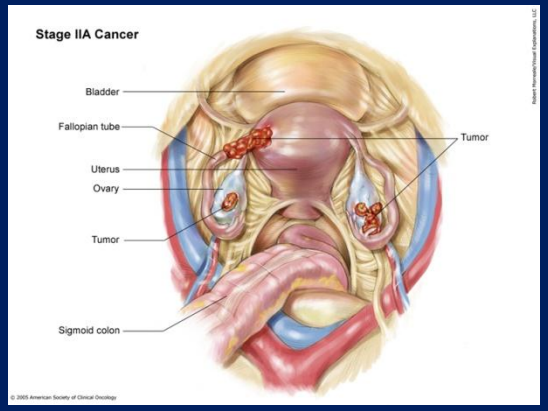
Stage I Ovarian Cancer

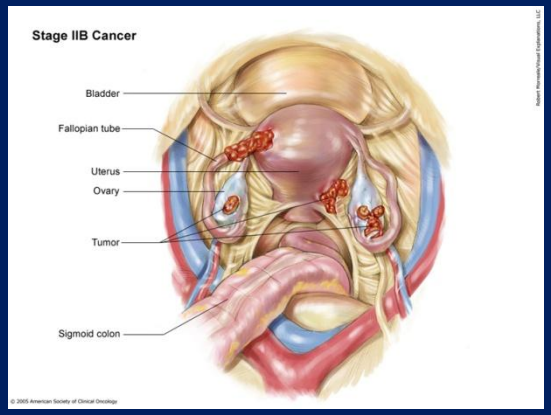


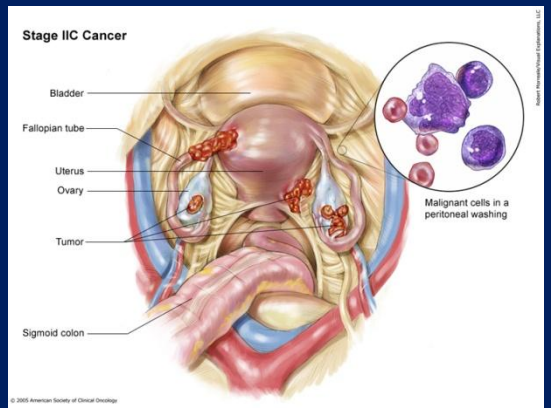


- Tumour is encapsulated and limited to ovaries
- No spread to lymph nodes or other parts of the body

Stage II Ovarian Cancer

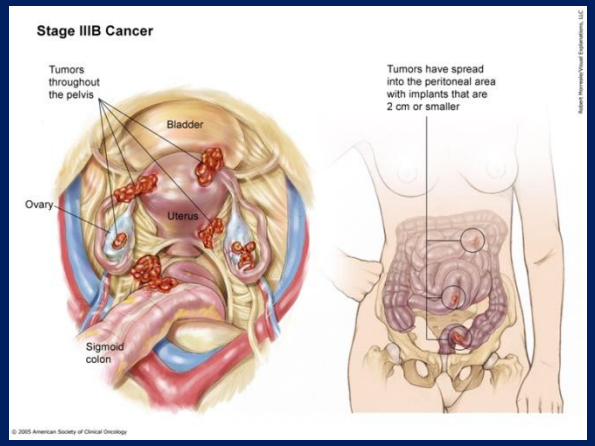


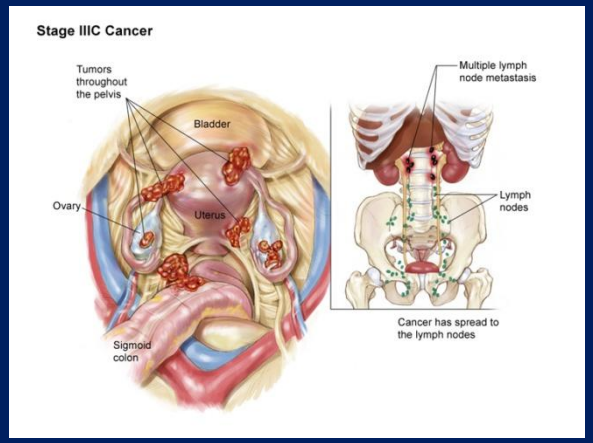




- Cancer is in one or both ovaries and has spread to the pelvis
- Cancer has spread to the uterus or fallopian tubes
- No spread to lymph nodes or other parts of the body

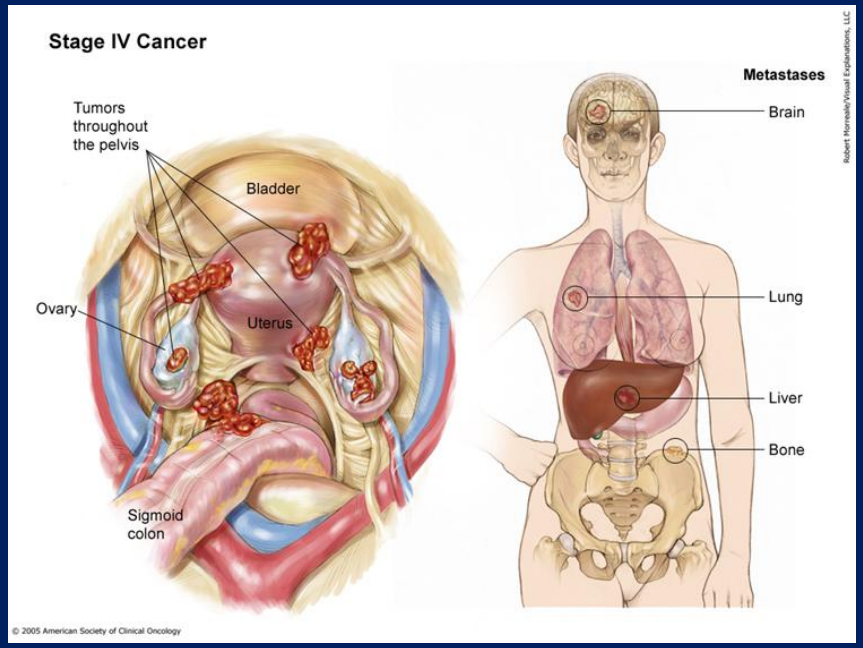
Stage III Ovarian Cancer





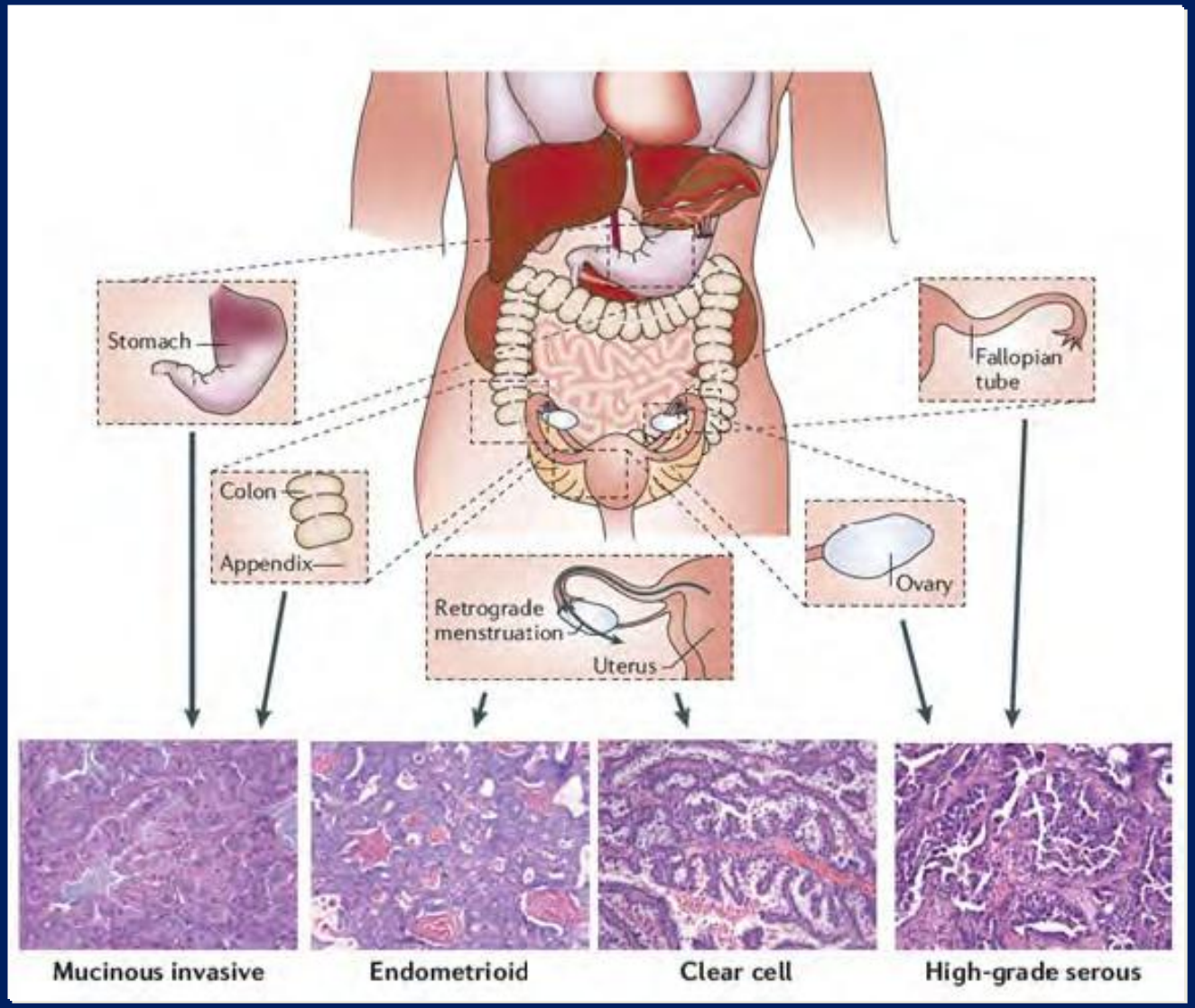
- Cancer is in one or both ovaries
- Cancer has spread beyond the pelvis into abdominal cavity
- Cytology -/+

Stage IV Ovarian Cancer



- Cancer has spread to distant organs
- Treatment includes surgery and IV or intraperitoneal chemotherapy

Cellular Classification



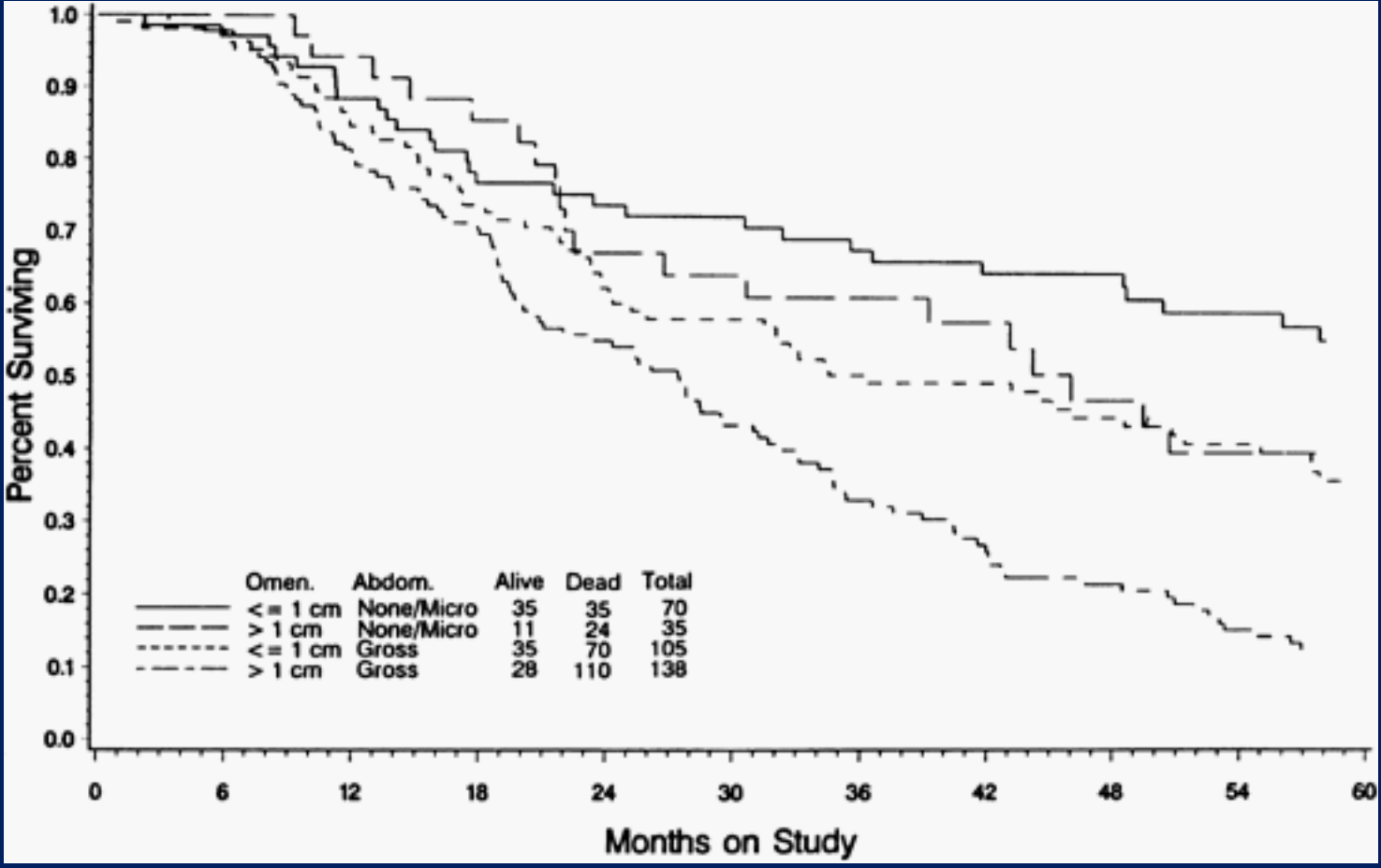
Prognostic Features

- FIGO Stage
- Histologic subtype (mucinous and clear cell worse)
- Histologic grade
- Age (Older worse)
- Performance status
- Disease volume prior to any surgical debulking
- Malignant ascites (or positive peritoneal washings)
- Ruptured capsule
- Dense ovarian adhesions
- Residual tumour following primary cyto-reductive surgery.
- CA 125 has a high correlation with survival when measured one month after the third course of chemotherapy for patients with stage III or stage IV disease

Surgery

- In the absence of extra-abdominal metastatic disease, definitive staging of ovarian cancer requires laparotomy.
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy and debulking to remove all or most of the tumour.
- The undersurface of the diaphragm should be visualised and biopsied and the abdominal peritoneum sampled; selective pelvic and para-aortic node sampling is required .
- If disease appears to be limited to the ovaries or pelvis, it is essential at laparotomy to examine and biopsy the diaphragm, both paracolic gutters, the pelvic peritoneum, para-aortic and pelvic nodes, and infracolic omentum, and to obtain peritoneal washings.

Impact of Debulking



Treatment: Stage I & Stage II

- Surgery

- Several treatment approaches that
  - systemic chemotherapy
  - careful observation without immediate treatment in selected patients (watchful waiting)

Results of a Randomised Trial in 923 Patients with High Risk Early Ovarian Cancer, Comparing Adjuvant Chemotherapy with No Further Treatment Following Surgery

Vergote, Trimbos, Guthrie et al

Early Ovarian Cancer (cont.)

- 923 patients accrued to ACTION (EORTC) and ICON 1 (MRC)
- ACTION: FIGO IA, IB (grades 2-3), IC, IIA (all grades), and all clear cell carcinomas
- ICON 1: Any patient in whom clinician was uncertain as to whether the patients should receive adjuvant chemotherapy.
- Randomisation between surgery alone and surgery plus platinum-based chemotherapy
- Survival was primary end point

Early Ovarian Cancer – DFS (mths)

	ICON 1	ACTION
	477	448
Observation	52	46
Chemotherapy	74	60

Combined HR 0.64, p = 0.001

Absolute difference at 5 years 11% (65% vs 76%)

Early Ovarian Cancer - Survival

	ICON 1	ACTION
	477	448
Observation	42	33
Chemotherapy	60	45

Combined HR = 0.68, p = 0.01

Absolute difference at 5 years 7% (75% vs 82%)

Early Ovarian Cancer - Conclusion

There is a survival advantage for all subgroups of patients with early stage ovarian cancer treated after surgery with platinum-based chemotherapy

Treatment: Stage III Disease

- Radical Debulking Surgery
- Systemic Chemotherapy: Paclitaxel and Platinum
- Combination chemotherapy regimens containing platinum have been shown to produce higher response rates and, in some studies, have produced a prolongation of survival compared to drug regimens without platinum.
- A meta-analysis addressing this comparison in 1,400 patients revealed a strong trend in favour of platinum-containing combinations with respect to response, but not survival.

Treatment: Stage IV Disease

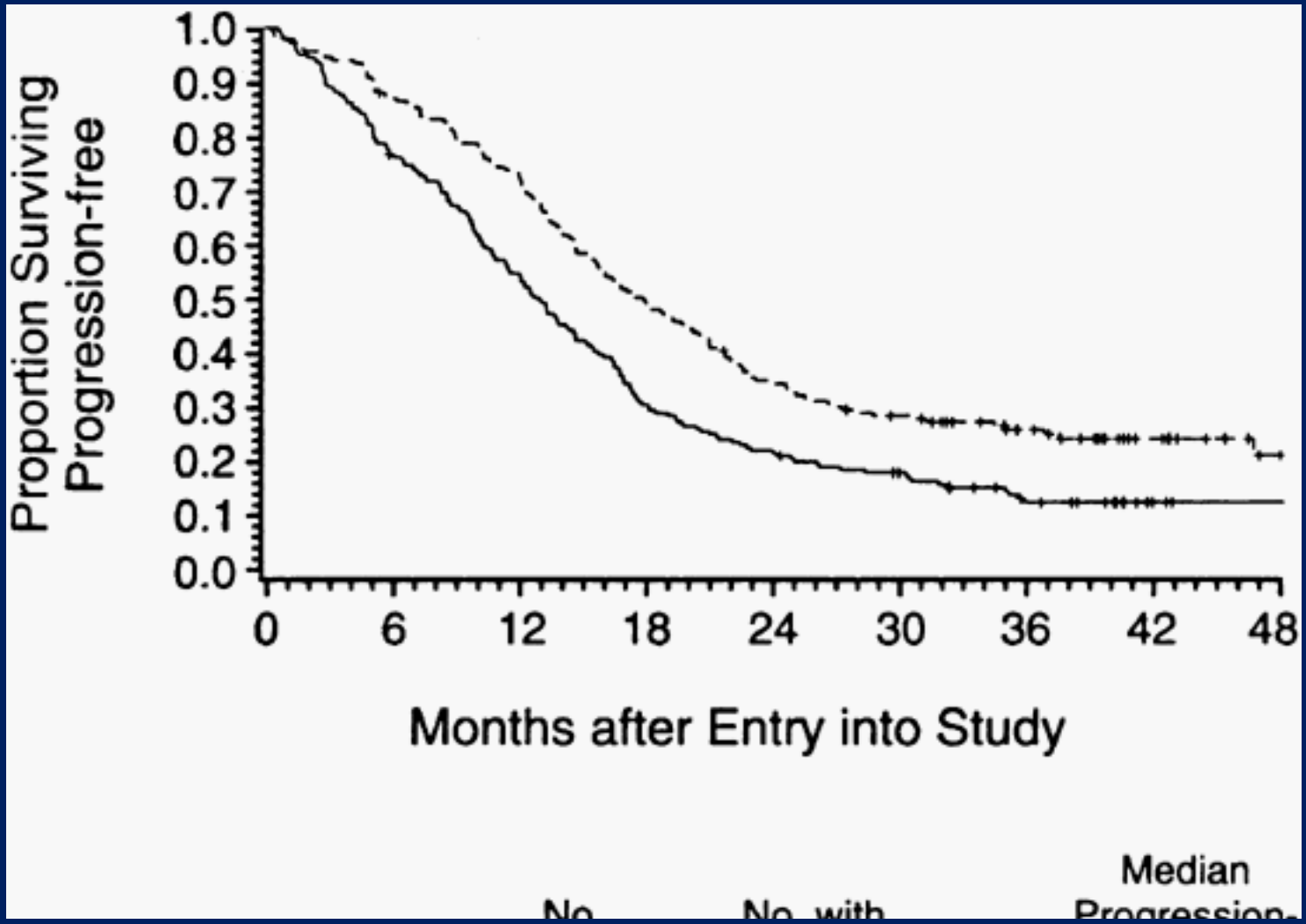
- Although many patients with stage IV disease undergo cytoreductive surgery, whether this improves survival has not been established.
- Intravenous paclitaxel (Taxol) plus intravenous cisplatin or intravenous carboplatin is commonly used.
- These patients should be considered for clinical trials involving novel therapies.

Ovarian Cancer: Initial Chemotherapy

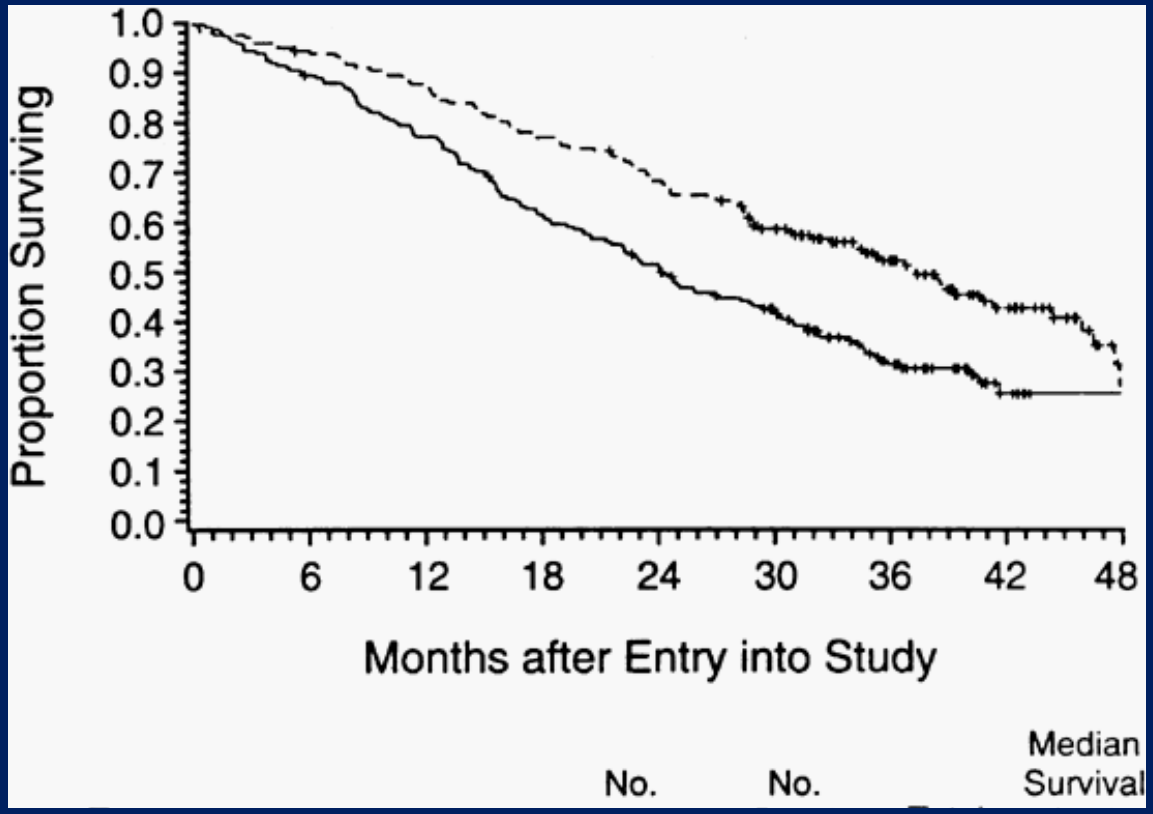
- Standard *frontline* chemotherapy is paclitaxel 175 mg/m^2 plus carboplatin AUC 6-7, every 21 days for 6 cycles
- Result of several studies over last decade
  - GOG 111[1] and OV 10[2]: paclitaxel/cisplatin vs cyclophosphamide/cisplatin
  - GOG 158[3] and AGO OVAR-3[4]: carboplatin instead of cisplatin

1. McGuire WP, et al. N Engl J Med. 1996;334:1-6. 2. Piccart MJ, et al. J Natl Cancer Inst. 2000;92:699-708. 3. Ozols RF, et al. J Clin Oncol. 2003;21:3194-3200. 4. du Bois AD, et al. J Natl Cancer Inst. 2003;95:1320-1329.

GOG 111: PFS


Proportion Surviving Progression-free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
Months after Entry into Study
Median

GOG 111: Survival



What About Alternative Taxane Therapy?

SCOTROC: Clinical Response*

Outcome, %	Paclitaxel/Carboplatin (n = 296)	Docetaxel/Carboplatin (n = 300)
CR	28	28
PR	31	30
ORR	**59**	**59**
NC	27	29
PD	10	9
Missing/not evaluable	4	4

*Similar results for patients with CA-125 elevation only.

Vasey P, et.al. J Natl Cancer Inst. 2004;96:1682-1691.

SCOTROC: Toxicity

Adverse Event, %	Paclitaxel/ Carboplatin	Docetaxel/ Carboplatin	*P* Value
Hematologic toxicity (grades 3-4)			
▪ Neutropenia	84	94	< .001
▪ Thrombocytopenia	10	9	.595
▪ Anemia	8	11	.112
Platelets	11	10	.27
Neuropathy (grades 2-4)	30	11	< .001

Vasey P, et.al. J Natl Cancer Inst. 2004;96:1682-1691.

Change in Schedule

Schema of JGOG 3016

Katsumata, Lancet 2009; 374: 1331

Ovarian Epithelial, Primary Peritoneal, or Fallopian Tube cancer
FIGO Stage II-IV

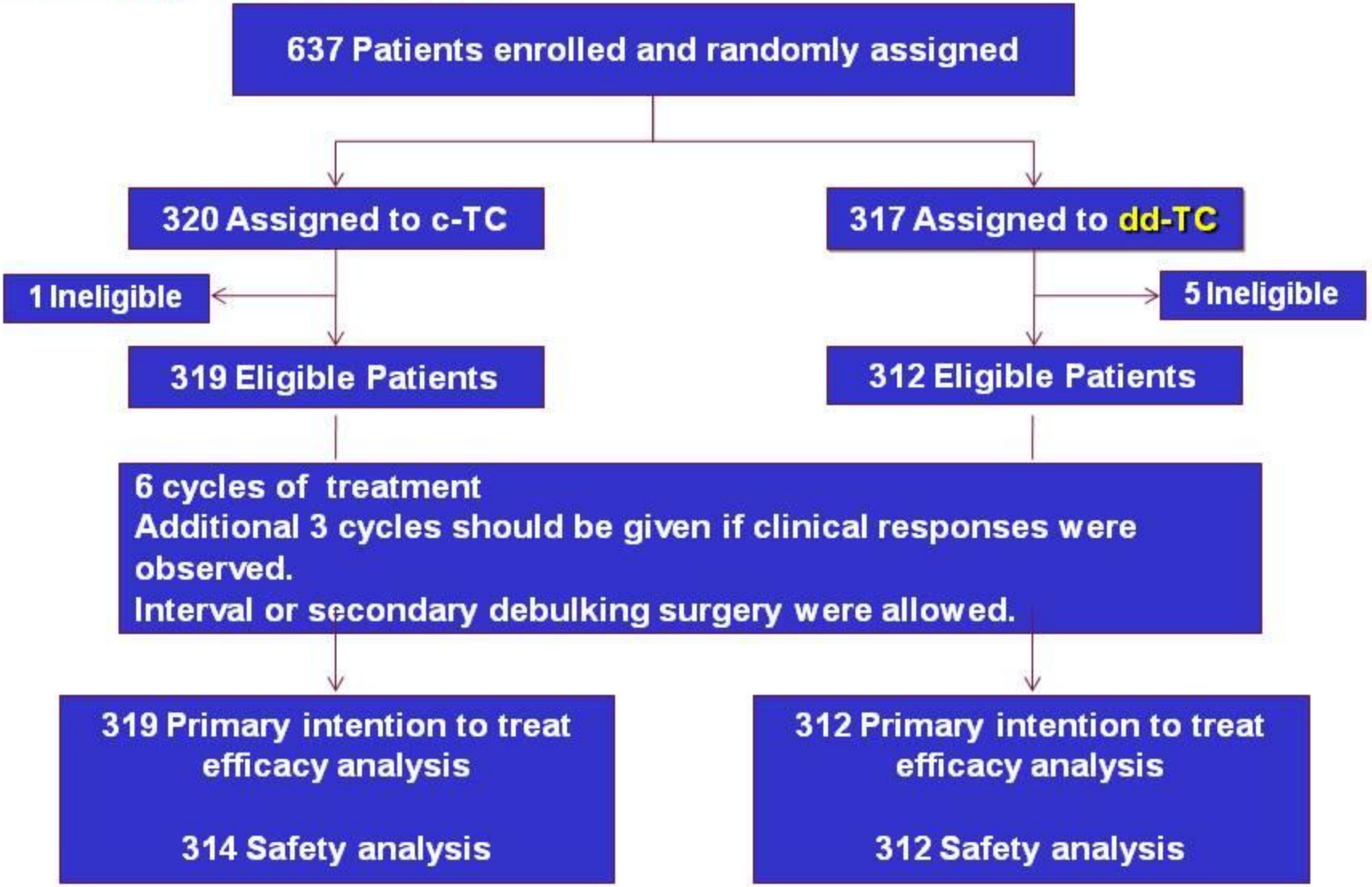
Randomization

Stratification;
- Residual disease: ≤1cm, > 1cm
- FIGO Stage : II vs. III vs. IV
- Histology : clear cell/mucinous vs.serous/others

Conventional TC (c-TC)
Paclitaxel 180mg/m², day 1
Carboplatin AUC 6.0, day 1
every 21 days for 6-9 cycles

Dose-dense weekly TC (dd-TC)
Paclitaxel 80mg/m², days 1,8,15
Carboplatin AUC 6.0, day 1
every 21 days for 6-9 cycles

Study Patients



Frequency of Grade 3 or 4 Adverse Events

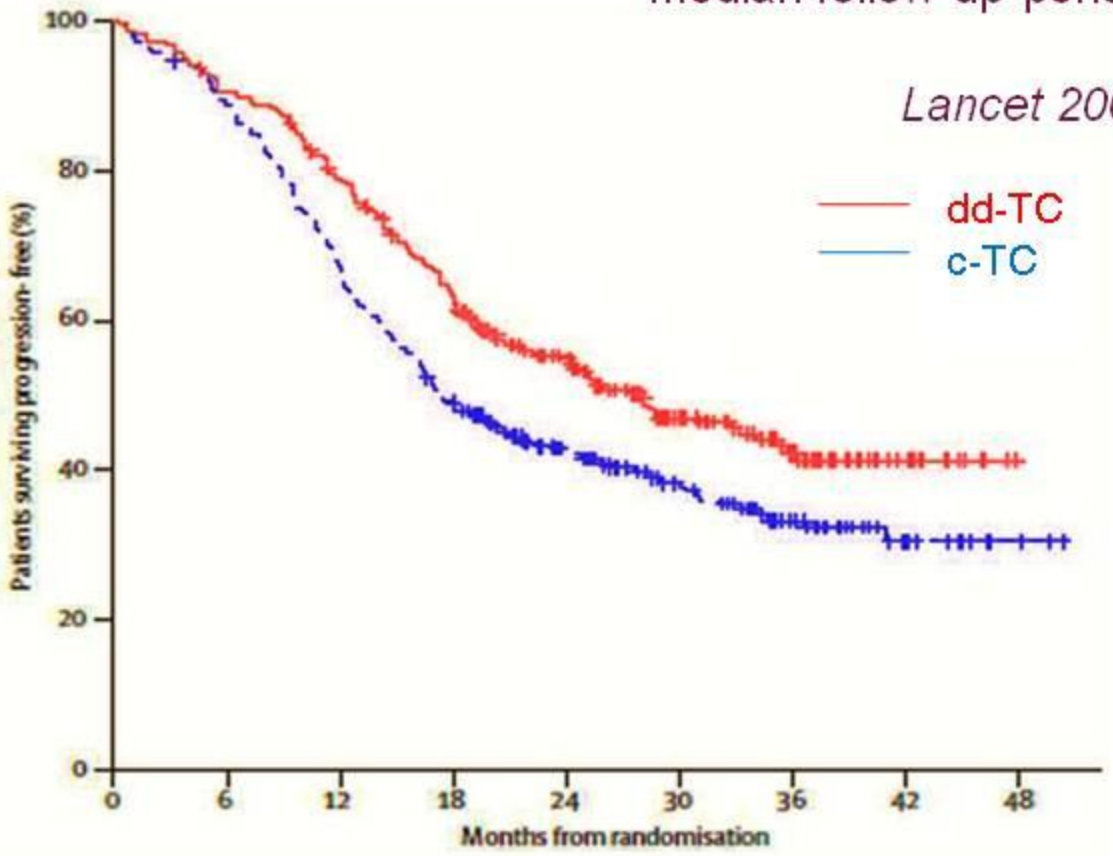
Evaluated by NCI-CTC ver.2.0

Adverse Event	c-TC (n = 314)	dd-TC (n = 312)	P value
	no. (%)		
Neutropenia	276 (88)	286 (92)	0.15
Thrombocytopenia	120 (38)	136 (44)	0.19
Anemia	137 (44)	214 (69)	< 0.0001
Febrile neutropenia	29 (9)	29 (9)	1.00
Neuropathy-motor	12 (4)	15 (5)	0.56
Neuropathy-sensory	20 (6)	21 (7)	0.87

JGOG3016: Progression-Free Survival

median follow-up period: 29 months

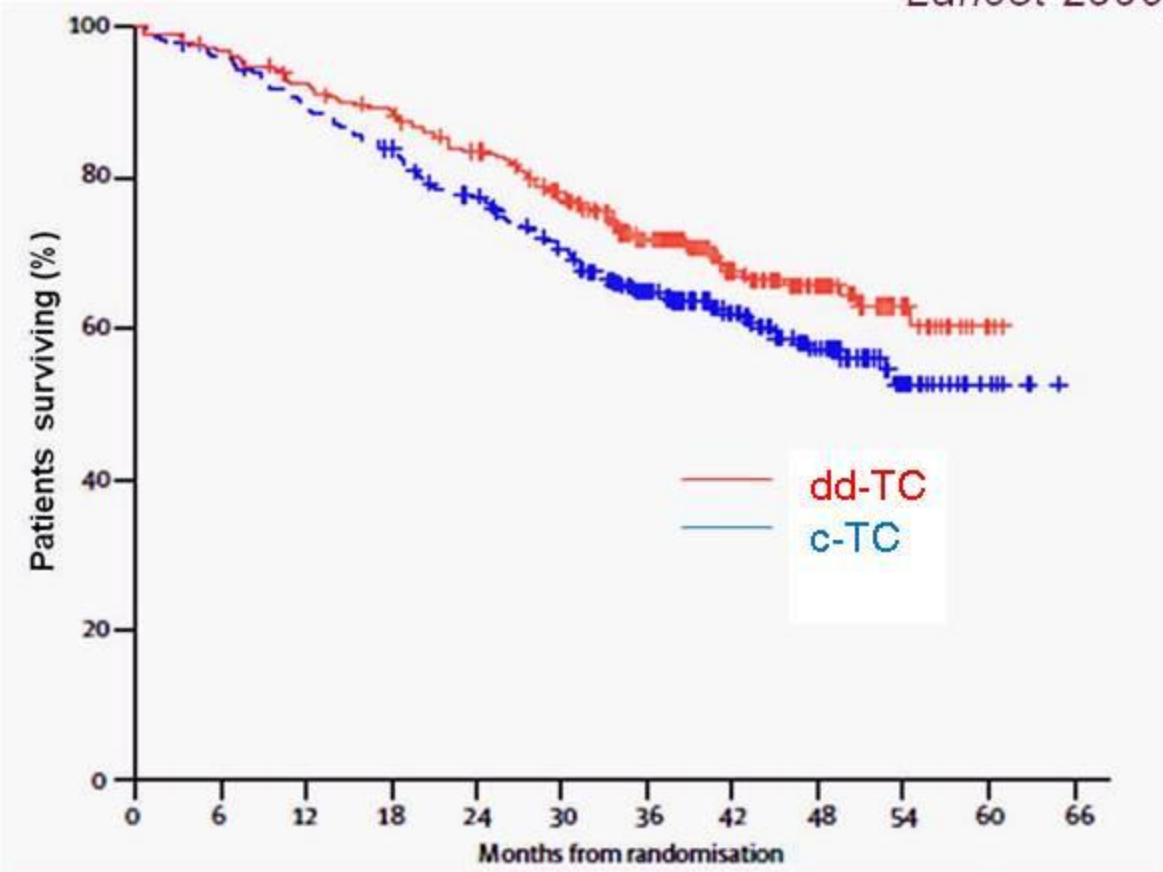
Lancet 2009; 374: 1331–38



Treatment	n	Event	Median PFS	*P* value	HR	95%CI
dd-TC	312	160	28.0 mos.	0.0015	0.714	0.581-0.879
c-TC	319	200	17.2 mos.			

JGOG3016: Overall Survival

Lancet 2009; 374: 1331–38



Treatment	n	Event	3-yr survival	*P* value	HR	95%CI
dd-TC	312	96	72.1%	0.032	0.75	0.57-0.98
c-TC	319	124	65.1%			

JGOG 3016 Update

- The analysis included eligible 631 patients.
- At 6.4 years of median follow-up:

	dd-TC	C-TC	P-value
Median PFS	28.1	17.5	0.0037
5-yr OS	58.6%	51.0%	0.0448

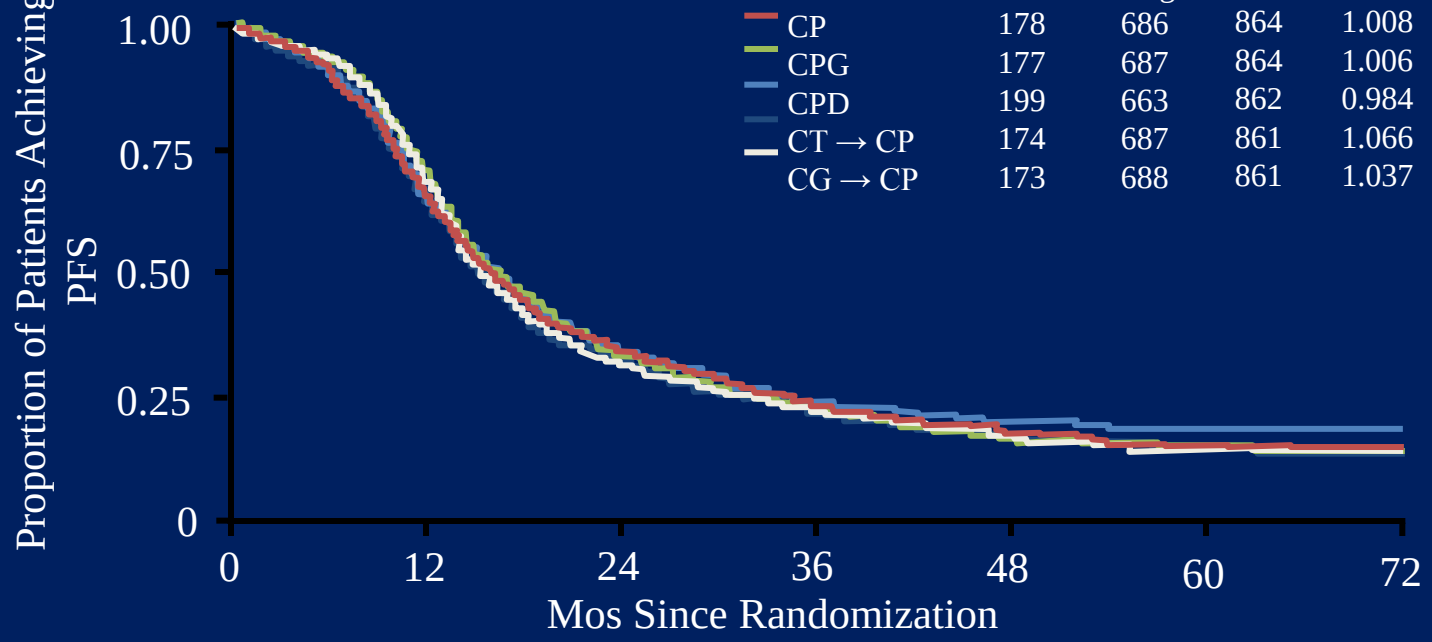
Will Adding a Third Drug Help?

GOG0182: Pac/Carbo vs Triplet or Sequential Doublet Combinations (Ph III)

- Paclitaxel/carboplatin x 8 (control)
- Paclitaxel/carboplatin/gemcitabine x 8
- Paclitaxel/carboplatin/PLD (4) x 8
- Topotecan/carboplatin x 4 $\rightarrow$ paclitaxel/carboplatin x 4
- Gemcitabine/carboplatin x 4 $\rightarrow$ paclitaxel/carboplatin x 4

Bookman MA, et al. J Clin Oncol. 2009;27:1419-1425.

GOG0182-ICON5: PFS

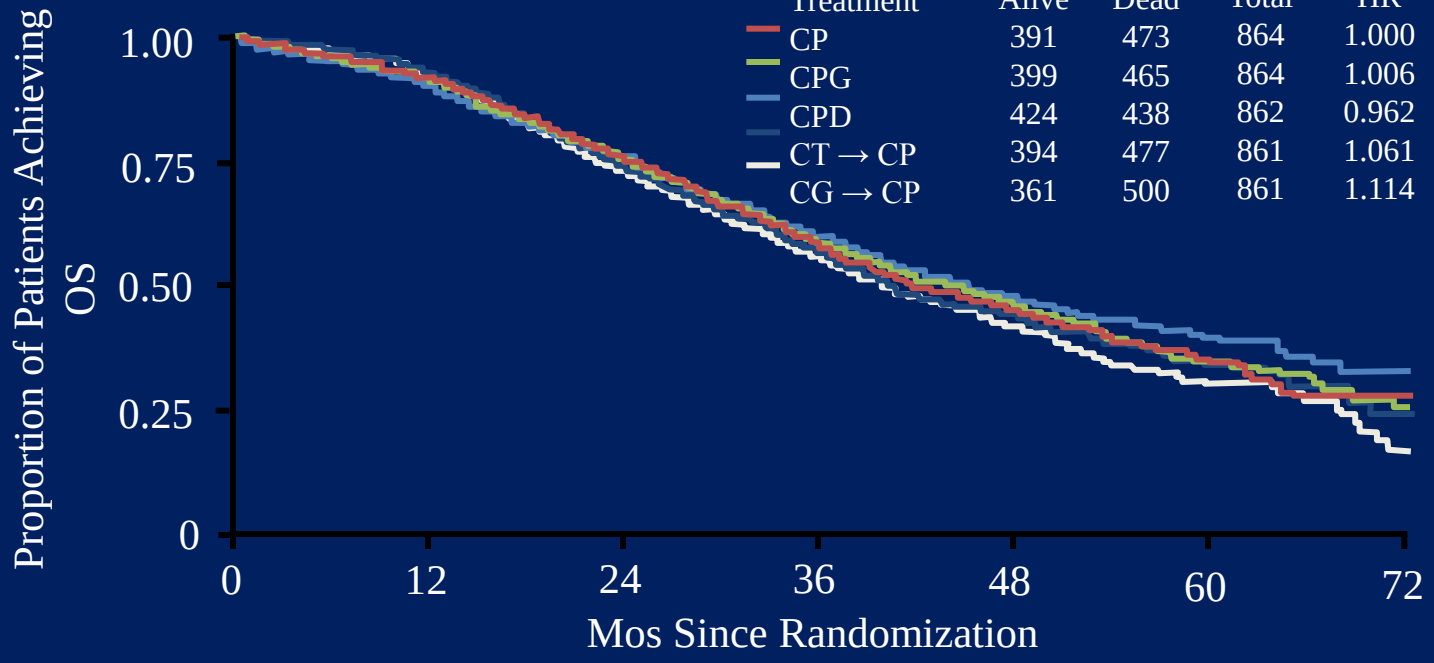


Treatment	Events: Cancer	Events: Prog	Events: Total	HR	Adjusted HR (95% CI)	*P*
CP	178	686	864	1.008	Reference Arm	
CPG	177	687	864	1.006	(0.924-1.143)	.610
CPD	199	663	862	0.984	(0.884-1.095)	.796
CT → CP	174	687	861	1.066	(0.958-1.186)	.239
CG → CP	173	688	861	1.037	(0.932-1.253)	.503

Patients at risk, n

CP	864	565	284	174	80	27
CPG	864	579	275	153	68	27
CPD	862	574	277	162	63	32
CT → CP	861	547	259	154	67	27
CG → CP	861	563	255	153	78	23

GOG0182-ICON5: Overall Survival



Treatment	Events: Alive	Events: Dead	Total	HR	Adjusted HR (95% CI)	*P*
CP	391	473	864	1.000	Reference arm	
CPG	399	465	864	1.006	(0.895-1.144)	.923
CPD	424	438	862	0.962	(0.836-1.085)	.462
CT → CP	394	477	861	1.061	(0.925-1.194)	.447
CG → CP	361	500	861	1.114	(0.982-1.264)	.093

Patients at Risk, n

CP	864	780	625	426	203	72
CPG	864	780	622	424	214	70
CPD	862	762	592	425	209	80
CT → CP	861	778	593	423	200	73
CG → CP	861	773	589	395	203	66

Other Recent 3-Drug Frontline Trials

Group(s)	Standard Arm	Experimental Arm (s)	N	Benefit
AGO/GINECO[1]	Paclitaxel/carboplatin (TC)	TC epirubicin	1282	NS
NSGO/EORTC NCIC CTG[2]	Paclitaxel/carboplatin (TC)	TC epirubicin	888	NS
Bolis[3]	Paclitaxel/carboplatin (TC)	TC topotecan	326	NS
AGO/GINECO[4]	Paclitaxel/carboplatin (TC)	TC → topotecan consolidation	1308	NS
AGO/GINECO NSGO[5]	Paclitaxel/carboplatin (TC)	TC gemcitabine	1742	NS
NCIC CTG EORTC/GEICO[6]	Paclitaxel/carboplatin (TC)	Cis topotecan → TC	819	NS

1. Du Bois A, et al. J Clin Oncol. 2006;24:1127-1135. 2. Kristensen G, et al. ASCO 2002. Abstract 805.
3. Scarfone G, et al. ASCO 2006. Abstract 5003. 4. Pfisterer J, et al. J Natl Cancer Inst. 2006;98:1036-1045.
5. Herrstedt J, et al. ASCO 2009. Abstract LBA5510. 6. Hoskins PJ, et al. ASCO 2008. Abstract LBA5505.

What About IP Therapy?

Role of IP Chemotherapy: Optimally Debulked Ovarian Cancer

GOG 104[1]	Improved outcome in CTX cisplatin-treated patients when cisplatin given IP (relative risk: 0.76)
GOG 114[2]	Improved outcome in patients when cisplatin administered IP (relative risk: 0.78)
GOG 172[3]	Improved outcome in patients when paclitaxel and cisplatin administered IP (relative risk: 0.73)

1. Alberts DS, et al. N Engl J Med. 1996;335:1950-1955.
2. Markman M, et al. J Clin Oncol. 2001;19:1001-1007.
3. Armstrong DK, et al. N Engl J Med. 2006;354:34-43.

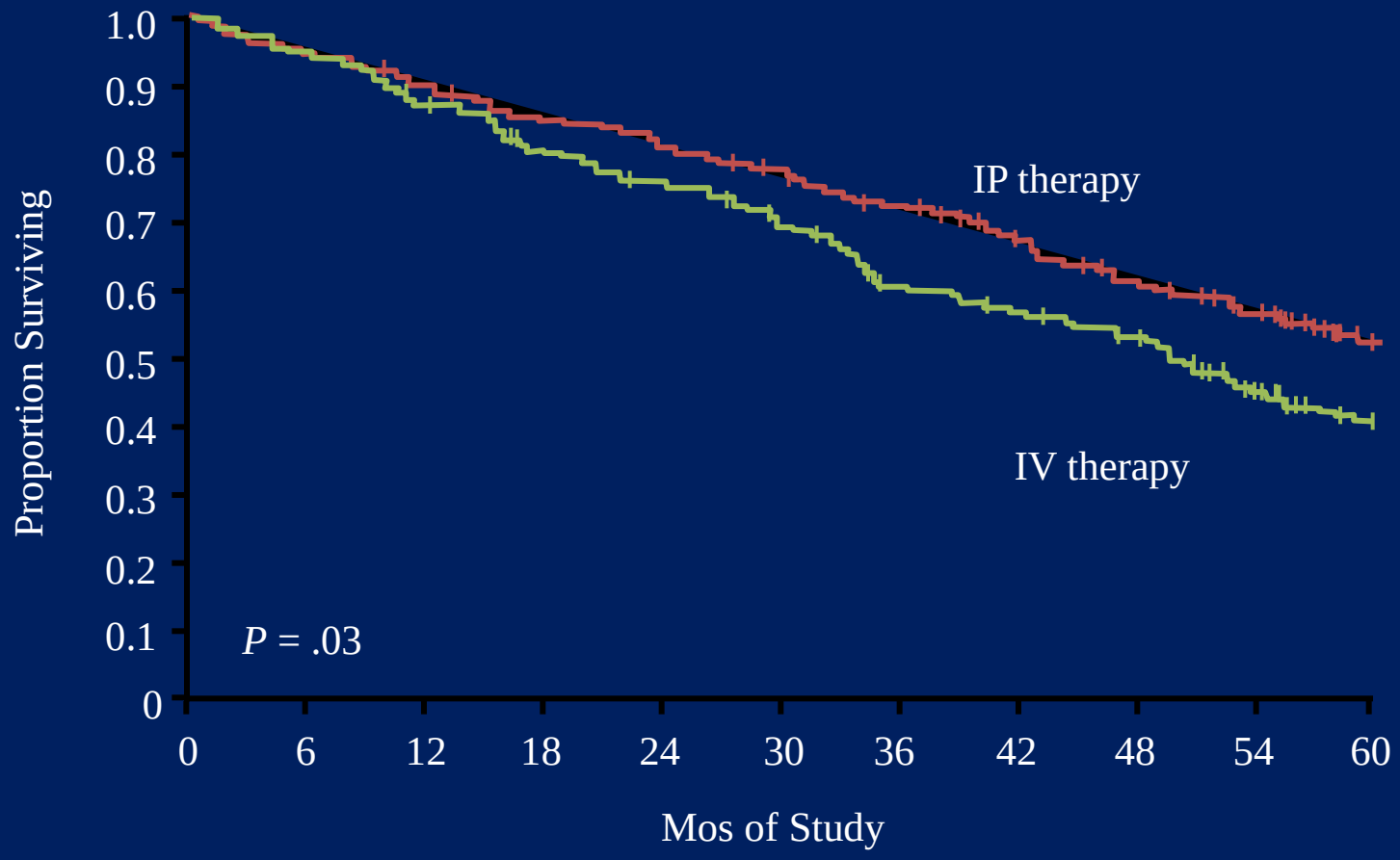
GOG 172: Survival

Outcome	IV	IP	RR	*P* Value
Median PFS, mos	18.3	23.8	0.80	.05
▪ Visible	15.4	18.3	0.81	
▪ Micro	35.2	37.6	0.80	
Median OS, mos	49.7	65.6	0.75	.03
▪ Visible	39.1	52.6	0.77	
▪ Micro	78.2	NA	0.69	

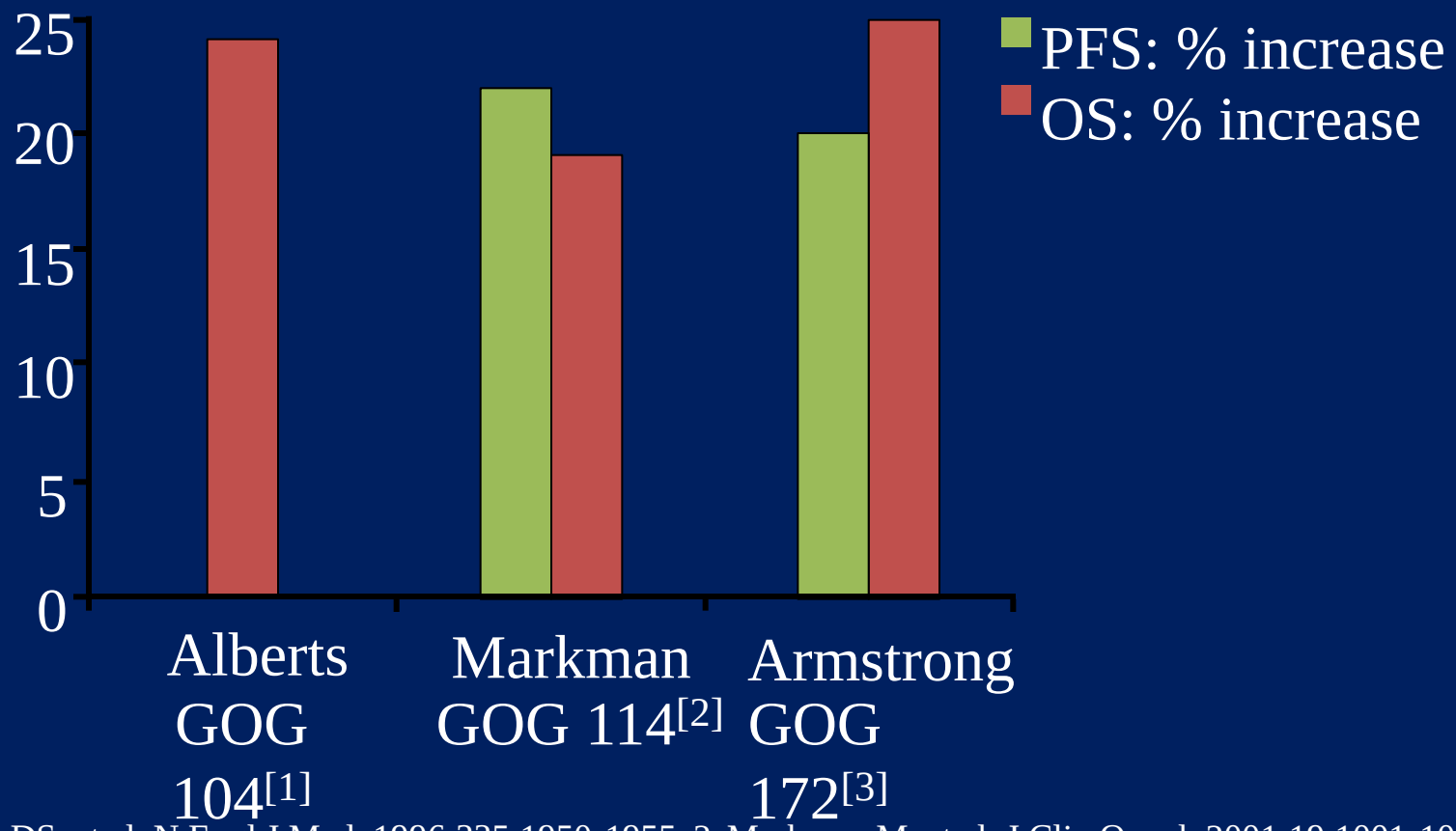
GOG 172: Survival

Outcome	IV	IP	RR	*P* Value
Median PFS, mos	18.3	23.8	0.80	.05
▪ Visible	15.4	18.3	0.81	
▪ Micro	35.2	37.6	0.80	
Median OS, mos	49.7	65.6	0.75	.03
▪ Visible	39.1	52.6	0.77	
▪ Micro	78.2	NA	0.69	

GOG 172: OS



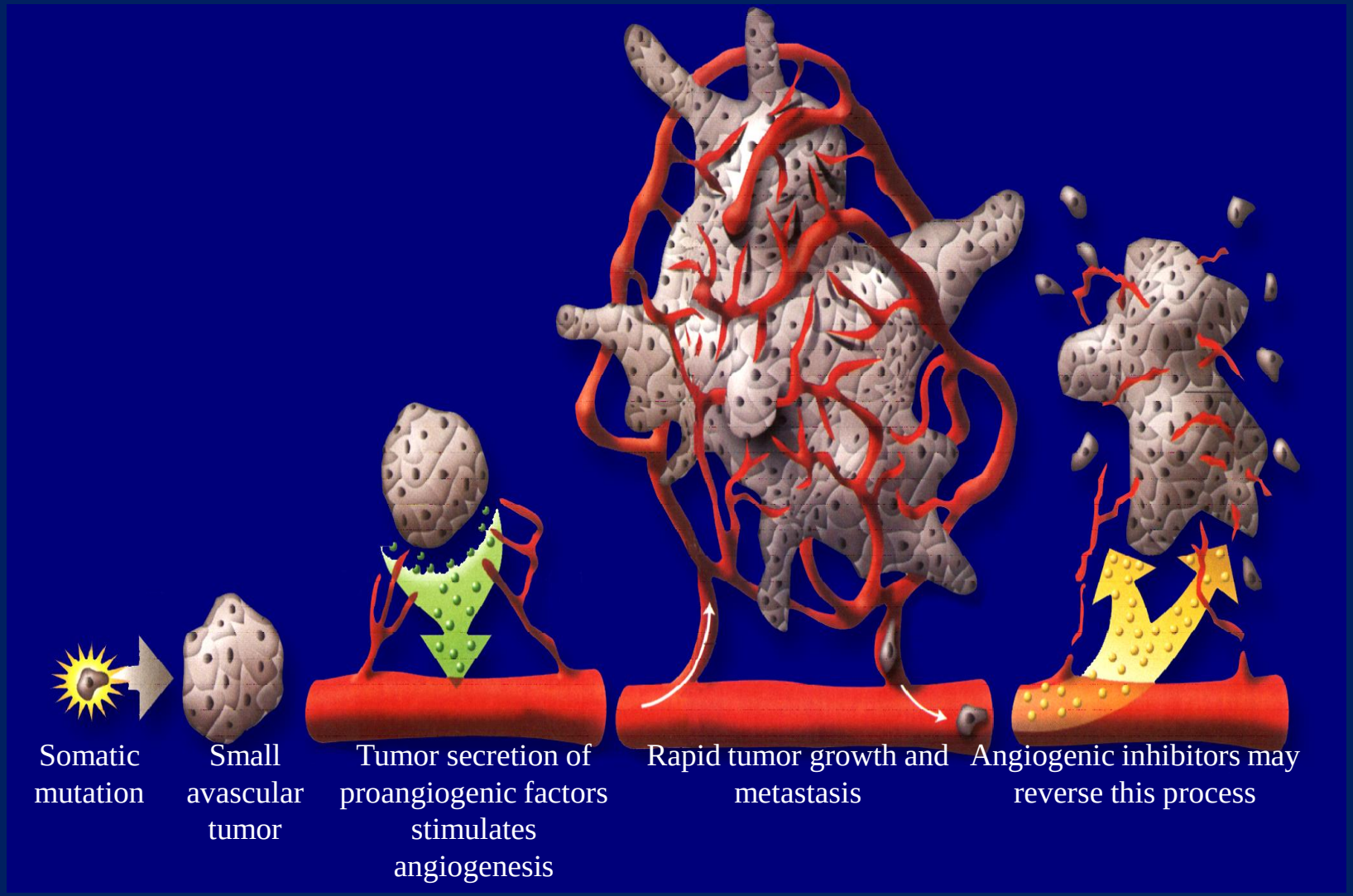
IP Compared With IV Chemotherapy Phase III Trials



1. Alberts DS, et al. N Engl J Med. 1996;335:1950-1955. 2. Markman M, et al. J Clin Oncol. 2001;19:1001-1007. 3. Armstrong DK, et al. N Engl J Med. 2006;354:34-43.

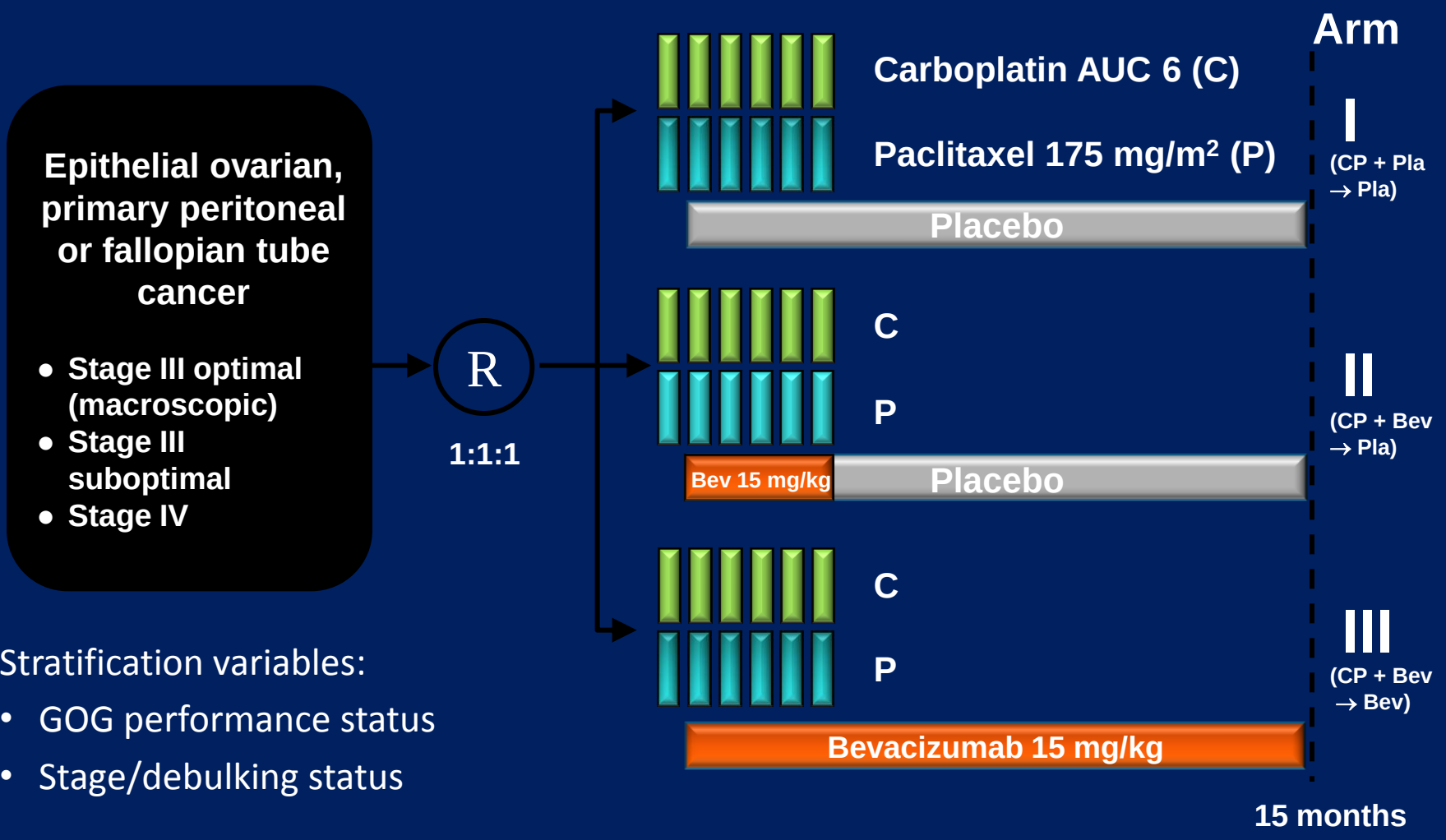
Will Adding a Targeted Therapy Help?

Angiogenesis as an Anticancer Treatment



Folkman J. N Engl J Med. 1971;285:1182-1186.

GOG-0218: Study design



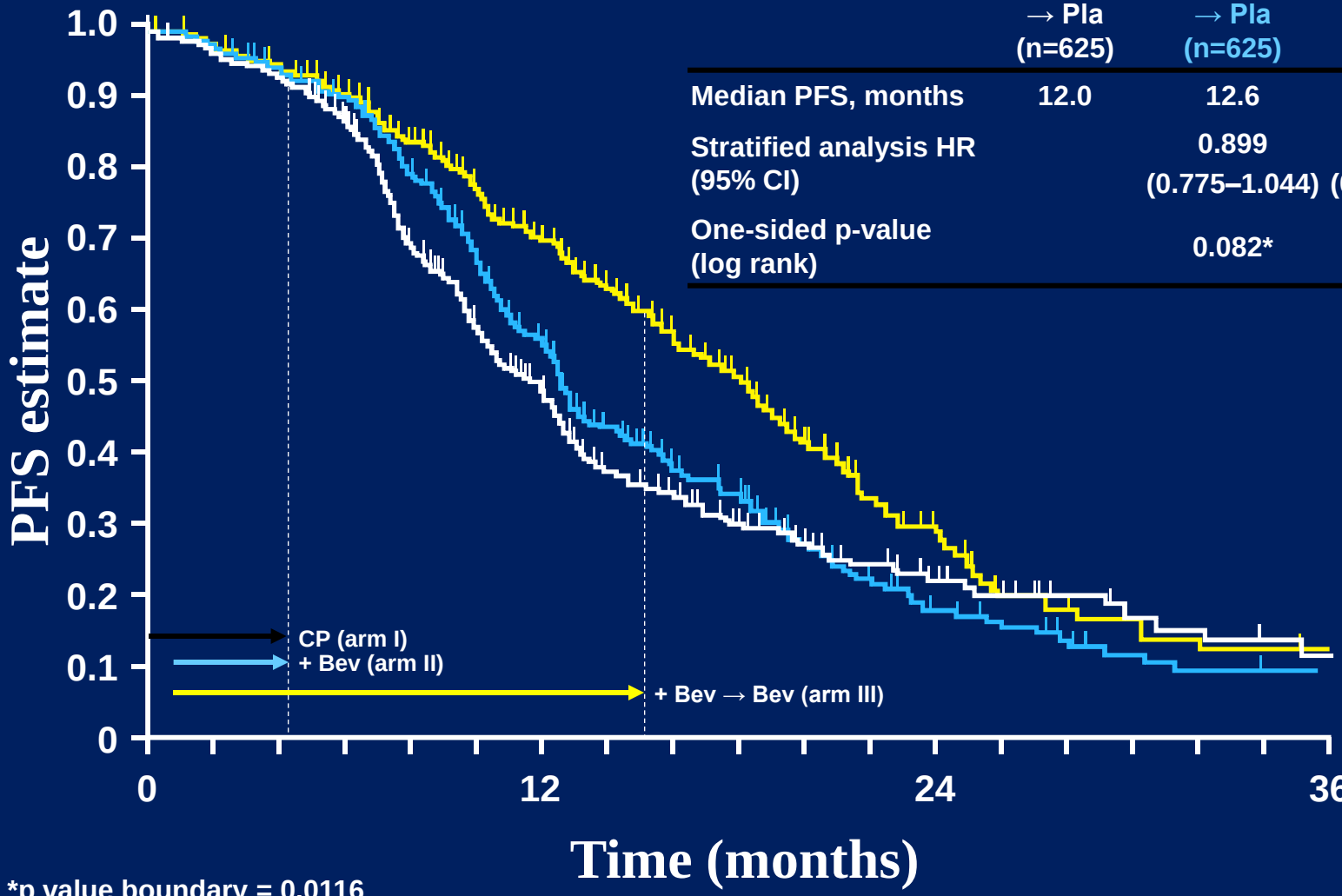
Stratification variables:

- GOG performance status
- Stage/debulking status

Burger et al. ASCO 2010

GOG-0218: Regulatory PFS analysis

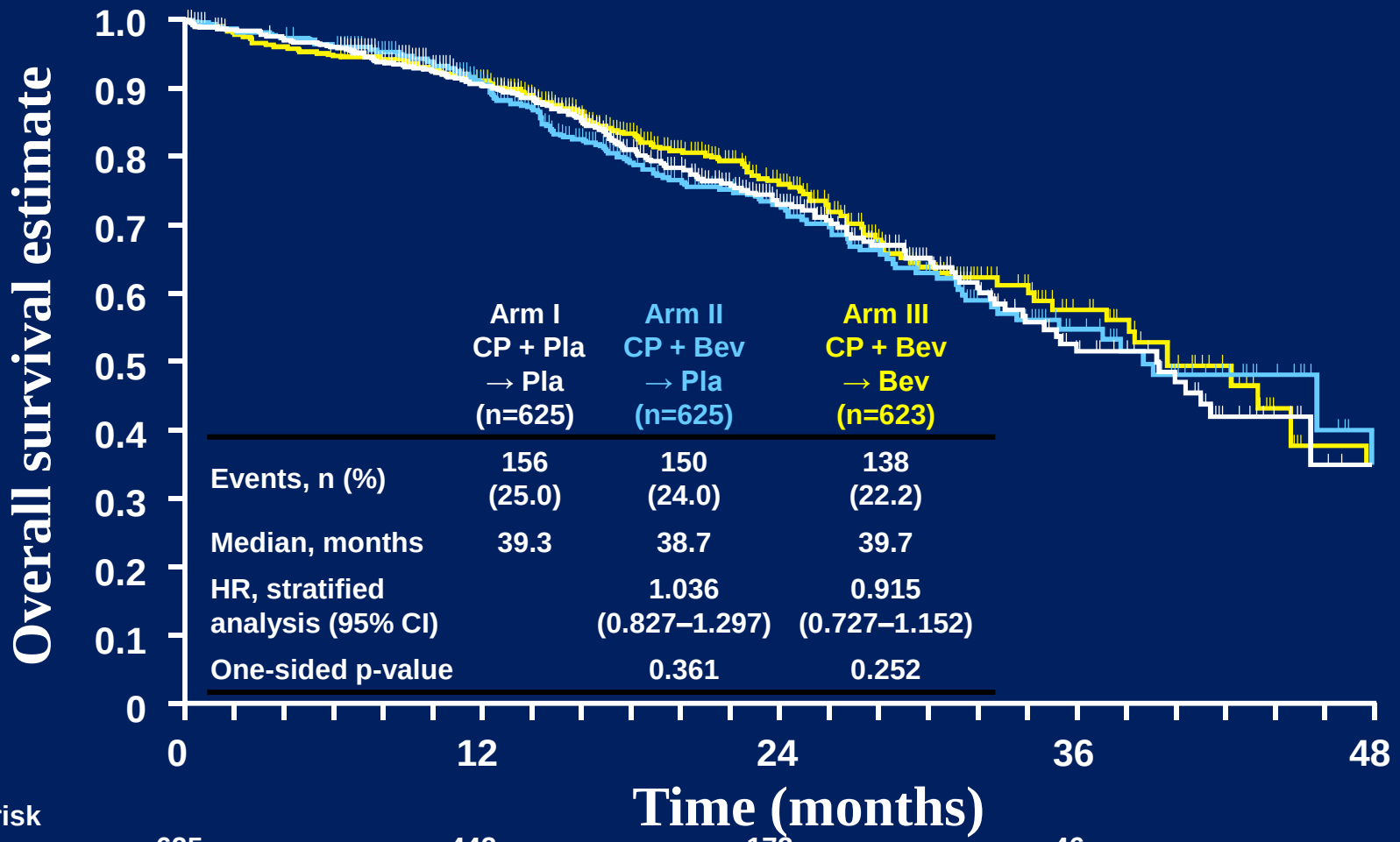
	Arm I CP + Pla → Pla (n=625)	Arm II CP + Bev → Pla (n=625)	Arm III CP + Bev → Bev (n=623)
Median PFS, months	12.0	12.6	18.0
Stratified analysis HR (95% CI)		0.899 (0.775–1.044)	0.645 (0.551–0.756)
One-sided p-value (log rank)		0.082*	<0.0001*



*p value boundary = 0.0116

Burger et al. SGO 2011; Roche data on file

GOG-0218: Overall survival



	Arm I CP + Pla → Pla (n=625)	Arm II CP + Bev → Pla (n=625)	Arm III CP + Bev → Bev (n=623)
Events, n (%)	156 (25.0)	150 (24.0)	138 (22.2)
Median, months	39.3	38.7	39.7
HR, stratified analysis (95% CI)		1.036 (0.827–1.297)	0.915 (0.727–1.152)
One-sided p-value		0.361	0.252

No. at risk				
Arm I	625	442	173	46
Arm II	625	432	162	39
Arm III	623	437	171	40

Burger at al. ASCO 2011

GOG-0218: Conclusions

- GOG-0218 met the primary objective of increasing PFS in the front-line treatment of advanced ovarian cancer
  - PFS with CP + Bev → continued single-agent Bev at 15 mg/kg for 15 months (arm III) was statistically superior to CP alone (arm I)
- Treatment was generally well tolerated, with a safety profile similar to that in bevacizumab studies in other tumour types
- CP + Bev → continued single-agent Bev at 15 mg/kg for a total of 15 months should be considered a standard front-line treatment option for advanced ovarian cancer

ICON7

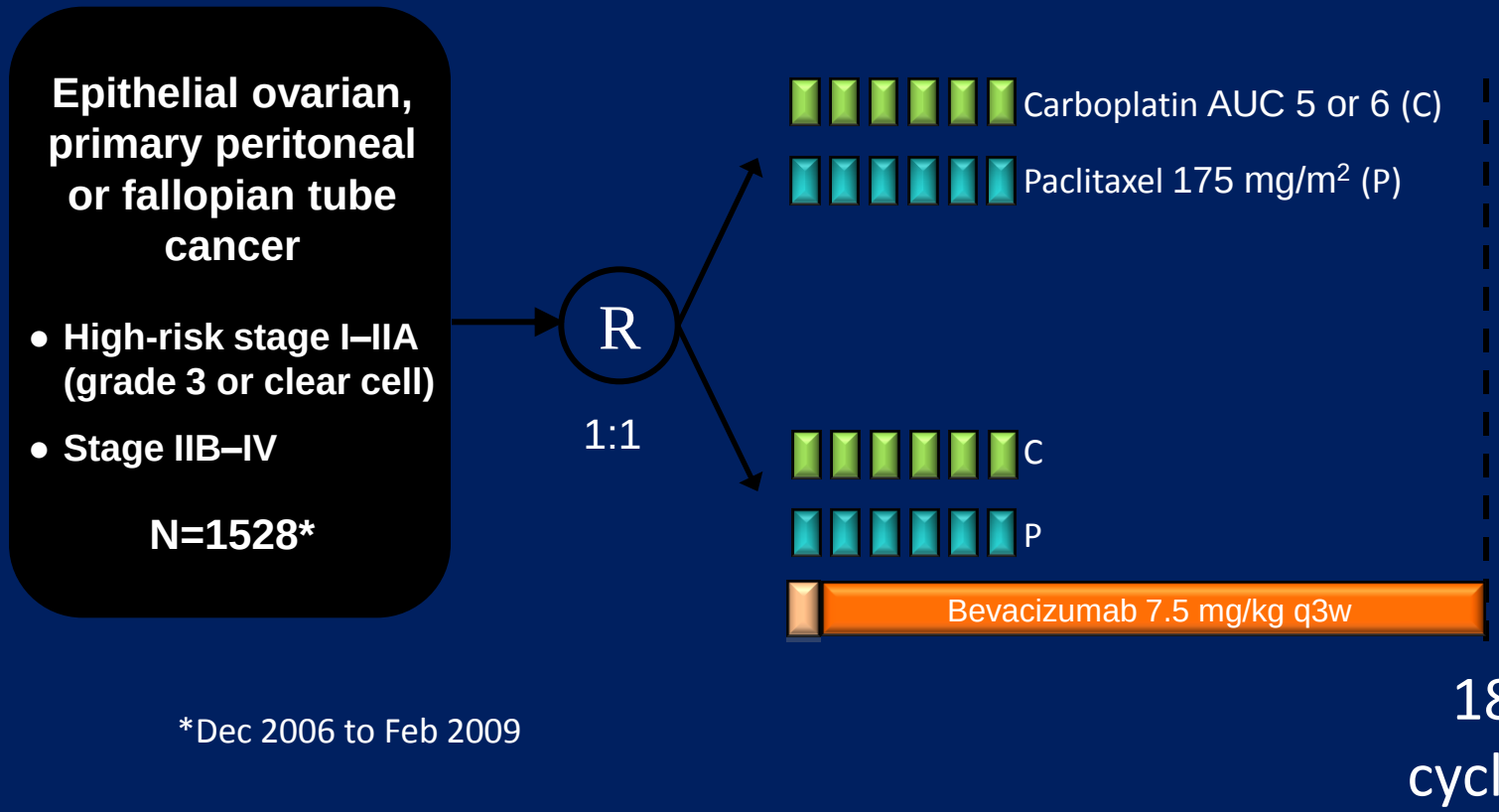
ICON7: A phase III Gynaecologic Cancer InterGroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers
ACRIN
AGO-AUST
AGO-OVAR
ANZGOG
EORTC
GEICO
GINECO
GOG
JGOG
MANGO
MITO
MRC/NCRI
NCI
NCIC CTG
NSGO
RTOG
SGCTG

ICON7
Bevacizumab in Ovarian Cancer

MRC Clinical Trials Unit

ICON7: Study design



*Dec 2006 to Feb 2009

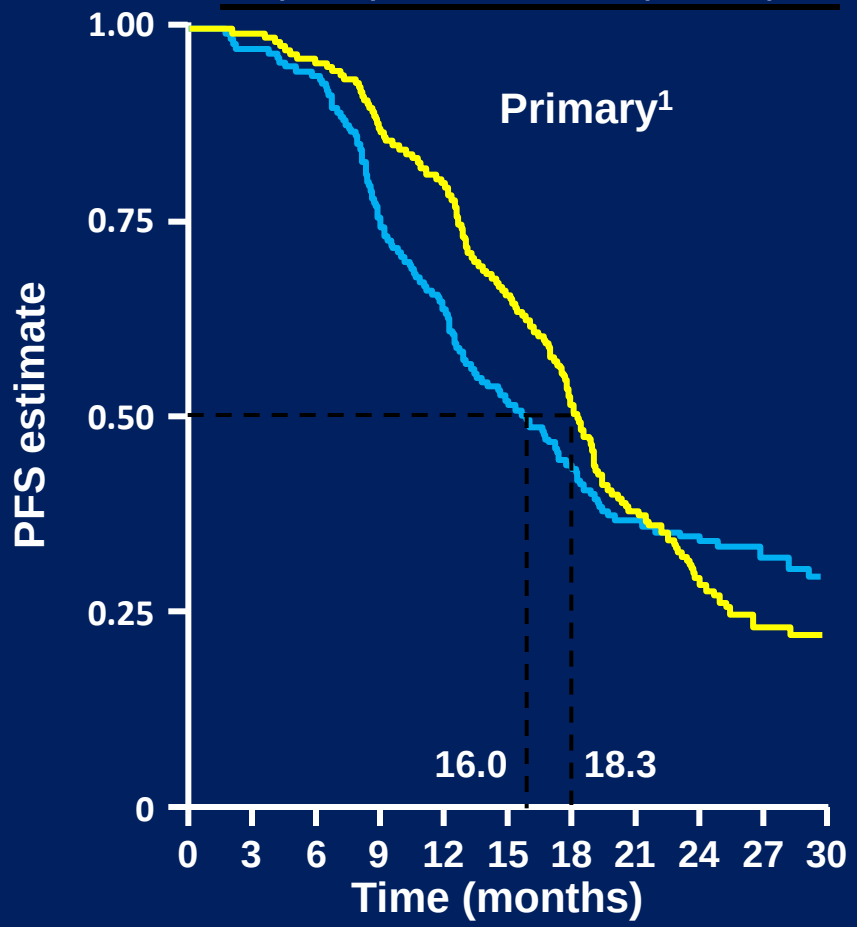
Stratification variables:

- Stage I–III debulked ≤1 cm vs stage I–III debulked >1 cm vs stage IV and inoperable stage III
- Intent to start treatment ≤/> 4 weeks after surgery
- GCIG group

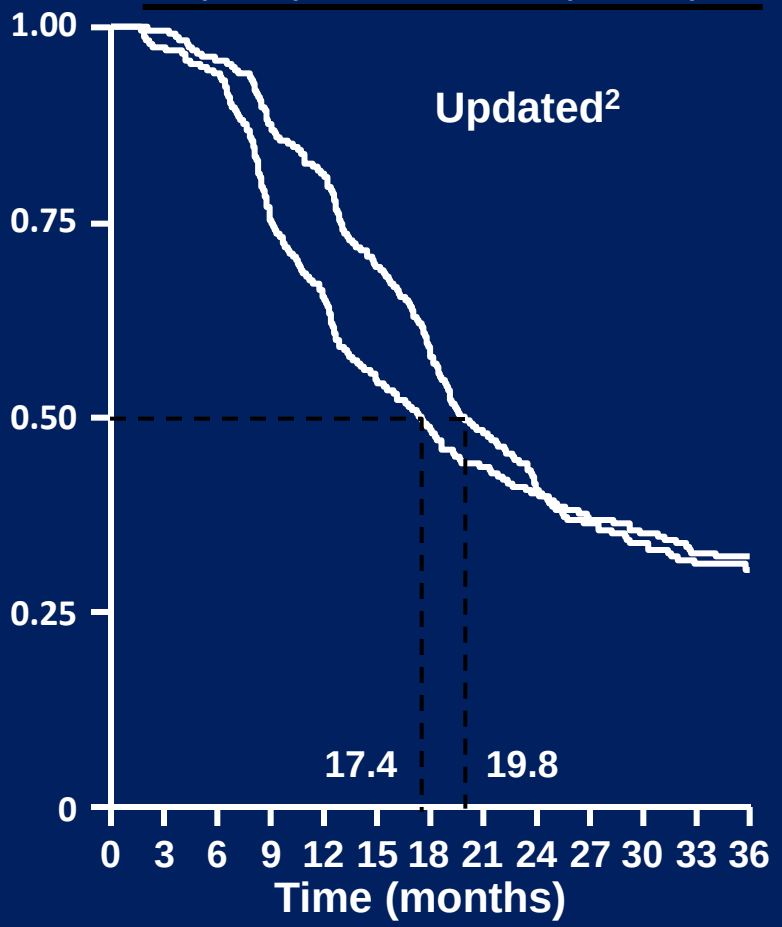
Perren et al. ESMO 2010

ICON7: PFS Analysis

	CP (n=764)	CP + Bev (n=764)
Events, n (%)	392 (51)	367 (48)
Median, months	16.0	18.3
Log-rank p-value	0.0010	
HR (95% CI)	0.79 (0.68–0.91)	

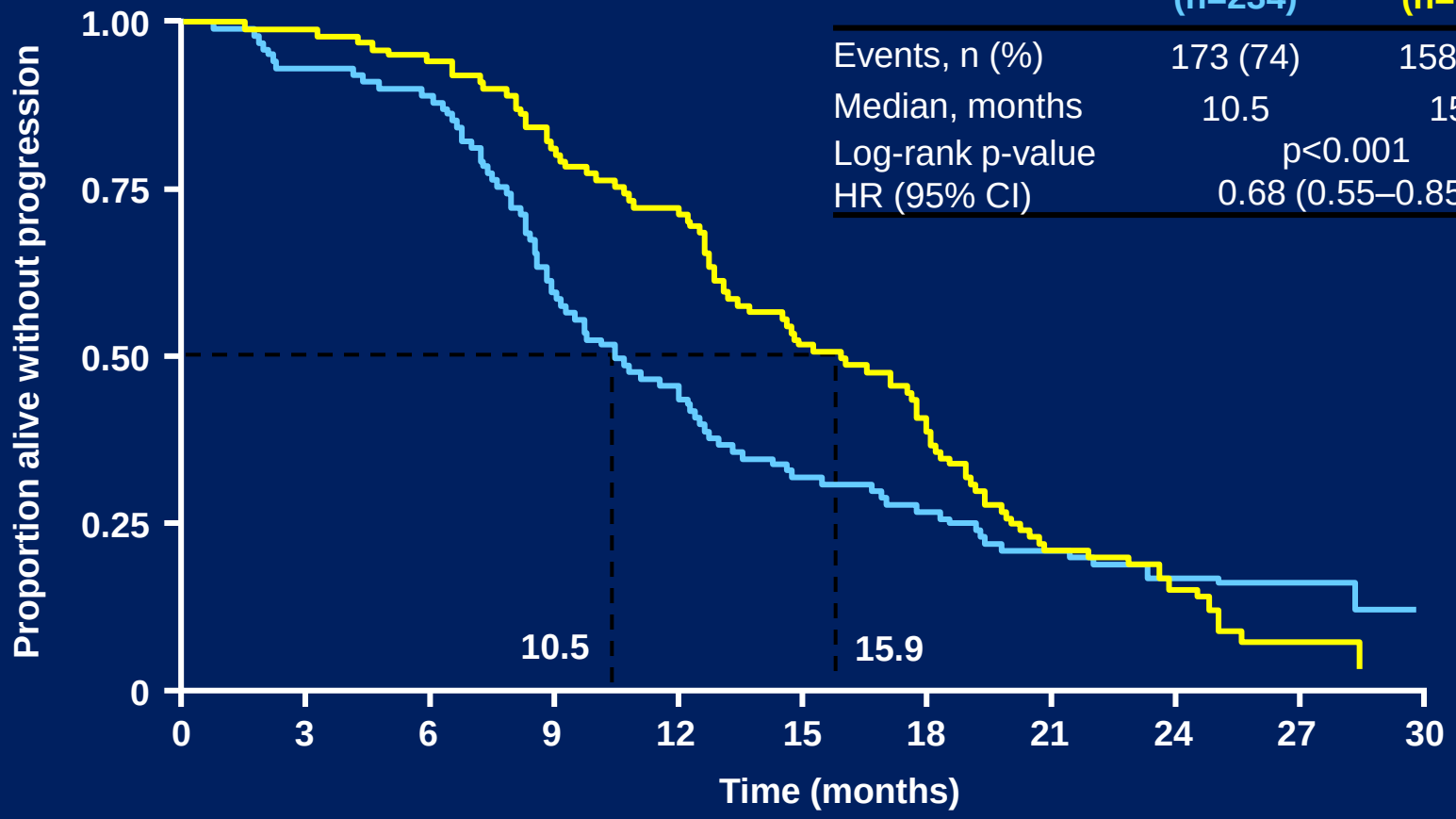


	CP (n=764)	CP + Bev (n=764)
Events, n (%)	464 (61)	470 (62)
Median, months	17.4	19.8
Log-rank p-value	0.039	
HR (95% CI)	0.87 (0.77–0.99)	



1. Perren et al. ESMO 2010; 2. Kristensen et al. ASCO 2011

ICON7: PFS (high-risk subgroup)



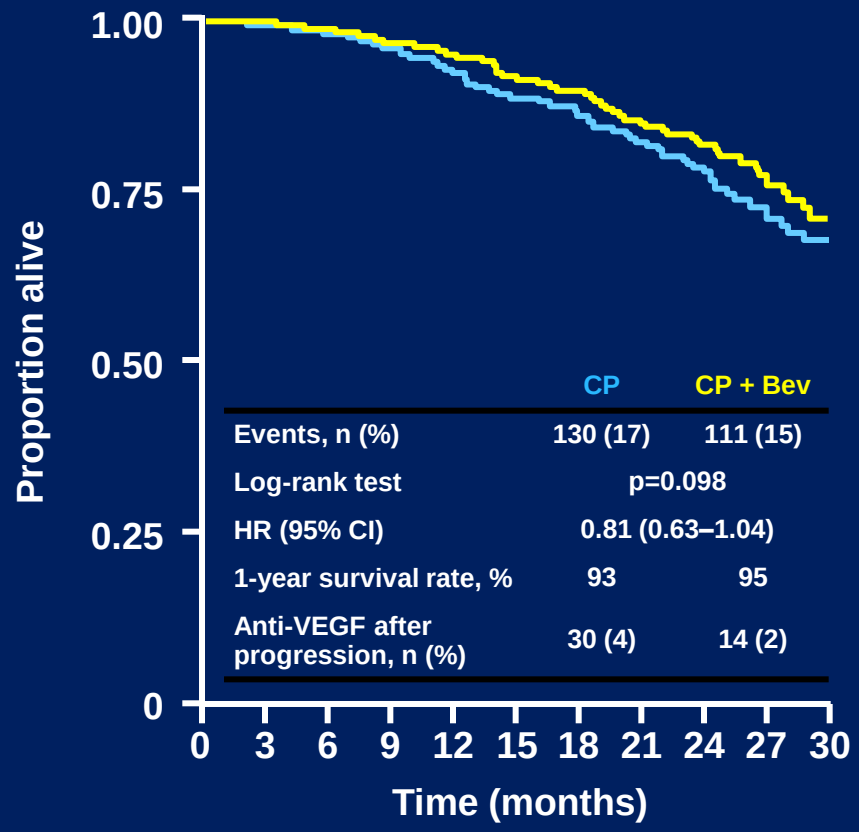
	CP (n=234)	CP + Bev (n=231)
Events, n (%)	173 (74)	158 (68)
Median, months	10.5	15.9
Log-rank p-value	p<0.001	
HR (95% CI)	0.68 (0.55–0.85)	

No. at risk						
CP	234	205	98	36	14	2
CP + Bev	231	213	159	56	10	1

Perren et al. ESMO 2010

ICON7: Overall survival

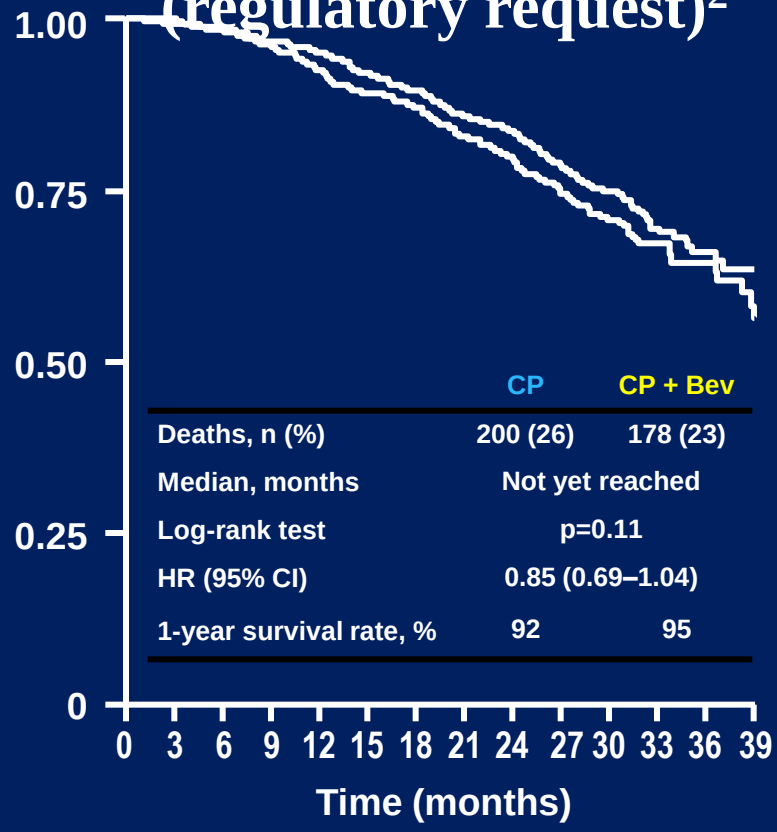
Preliminary analysis[1]



	CP	CP + Bev
Events, n (%)	130 (17)	111 (15)
Log-rank test	p=0.098	
HR (95% CI)	0.81 (0.63–1.04)	
1-year survival rate, %	93	95
Anti-VEGF after progression, n (%)	30 (4)	14 (2)

No. at risk											
CP	764	741	724	701	652	486	368	252	159	83	33
CP + Bev	764	753	737	716	678	525	404	259	162	89	40

Interim analysis (regulatory request)[2]

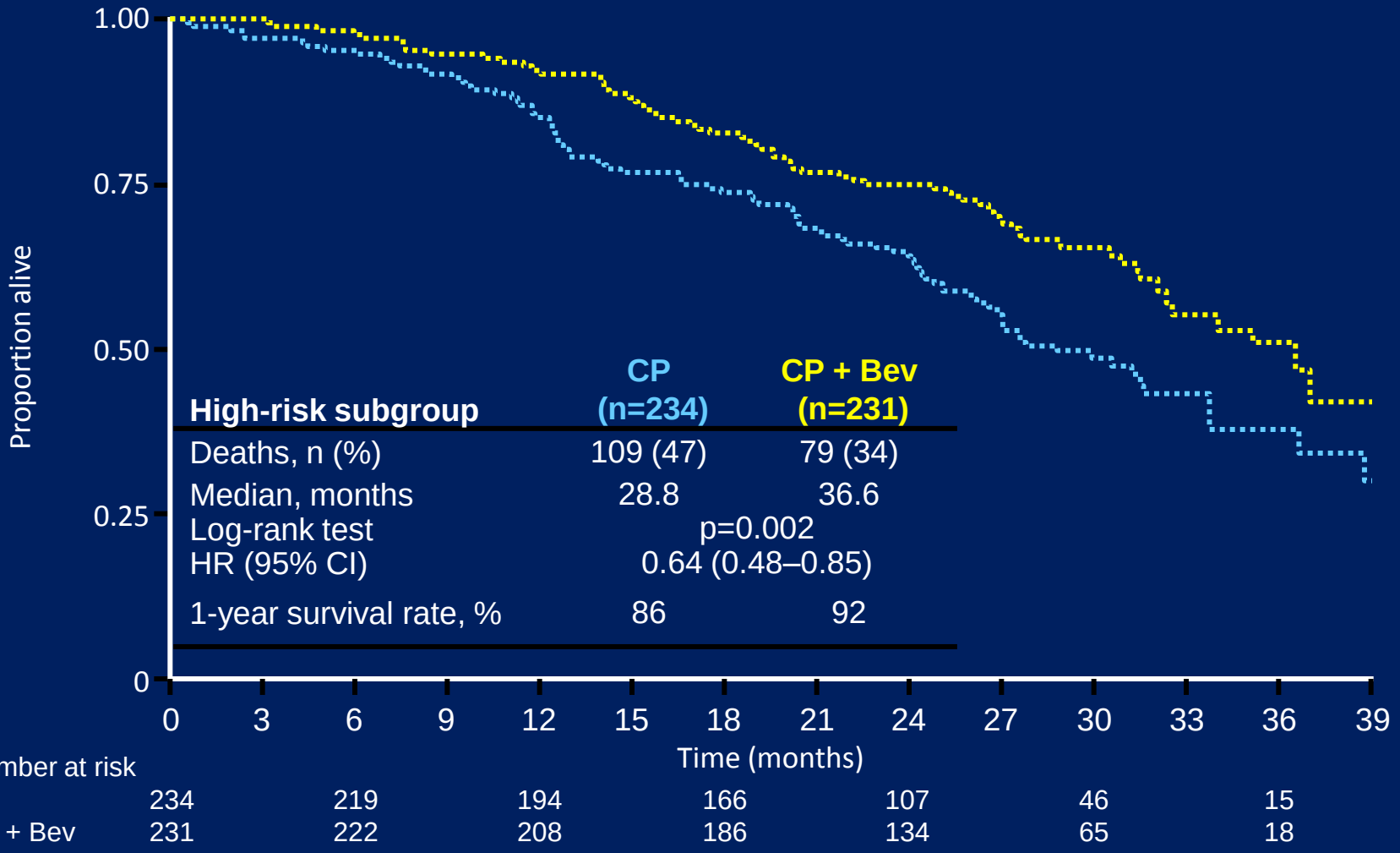


	CP	CP + Bev
Deaths, n (%)	200 (26)	178 (23)
Median, months	Not yet reached	
Log-rank test	p=0.11	
HR (95% CI)	0.85 (0.69–1.04)	
1-year survival rate, %	92	95

CP	764	741	724	703	672	646	623	542	421	304	212	132	71	26
CP + Bev	764	753	737	717	702	680	657	592	459	329	228	129	69	19

1. Perren et al. ESMO 2010; 2. Kristensen et al. ASCO 2011

ICON7: Overall survival (high-risk subgroup)



Bevacizumab is not approved as treatment for ovarian cancer

Kristensen et al. ASCO 2011

ICON7: Conclusions

- Primary objective of ICON7 was met
- Front-line bevacizumab (concurrent and continued) significantly improved PFS (HR=0.81; p=0.0041) vs chemotherapy alone
  - The benefit of bevacizumab appears to be greatest in patients with advanced-stage disease
- Treatment was well tolerated with no new safety concerns
- Second positive phase III trial of bevacizumab in ovarian cancer
- Results of ICON7 will influence treatment decisions and design of future research studies

Bevacizumab is not approved as treatment for ovarian cancer

Relapsed Disease

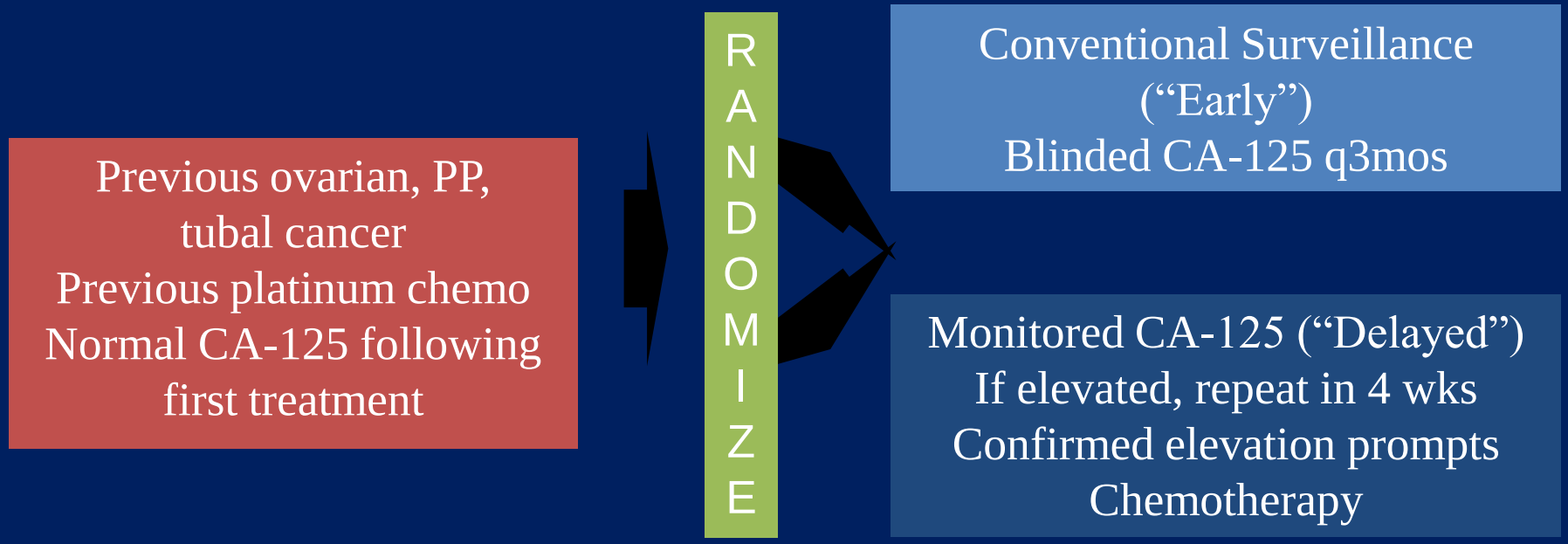
Background: Recurrent Ovarian Cancer

- Nearly 70% of advanced stage cancers relapse
- Treatment of recurrent disease is complex with a myriad options
- Elevation of CA-125 levels may be first indication of recurrent disease
- Marker reliability may be extraneously influenced by biologics
- Emerging data to inform clinicians on the role of observation vs treatment

Current Questions in Recurrent Disease

- How do you define recurrence?
  - Physical exam
  - Imaging
  - Chemical
- When do you treat?
  - Symptoms
  - Imaged lesions
  - Chemical

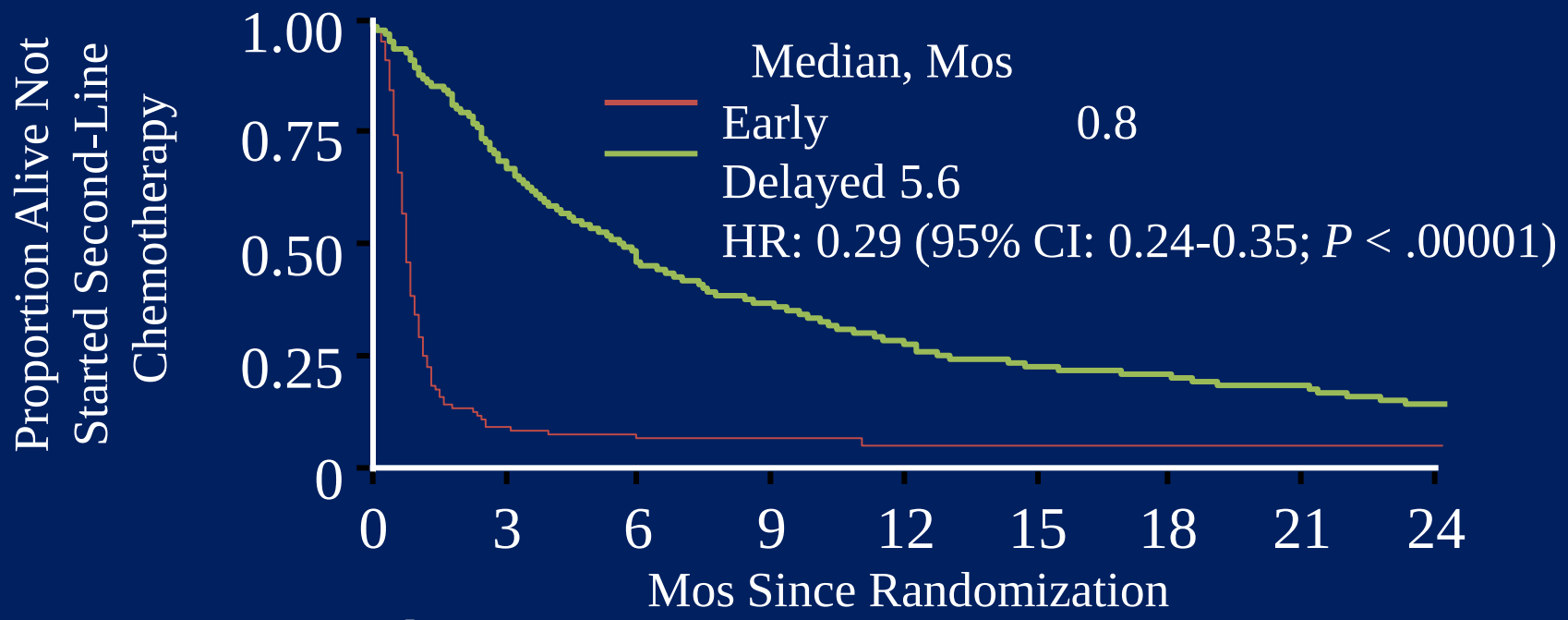
EORTC 55955: Schema



- Accrual goal: 1400
- Objectives: OS, TFS, QoL

When to Treat?

Time From Randomization to Second-Line Chemotherapy

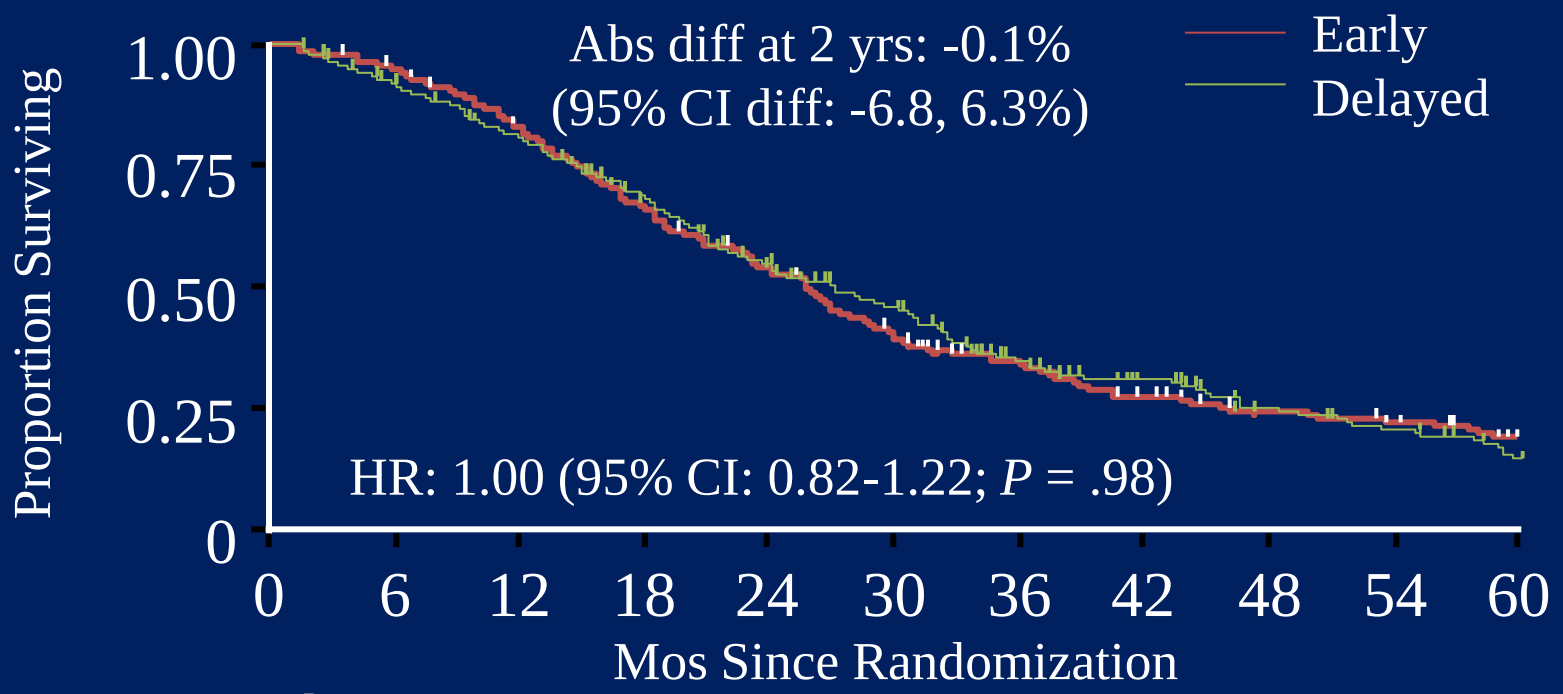


Patients at Risk, n

Early	265	23	16	14	11	11	10	10	9
Delayed	264	177	116	91	69	56	49	42	33

Rustin G, et al. ASCO 2009. Abstract 1. Reprinted with permission from the author.

Overall Survival



Patients at Risk, n

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. ASCO 2009. Abstract 1. Reprinted with permission from the author.

Pros & Cons of Treating CA-125 Increase

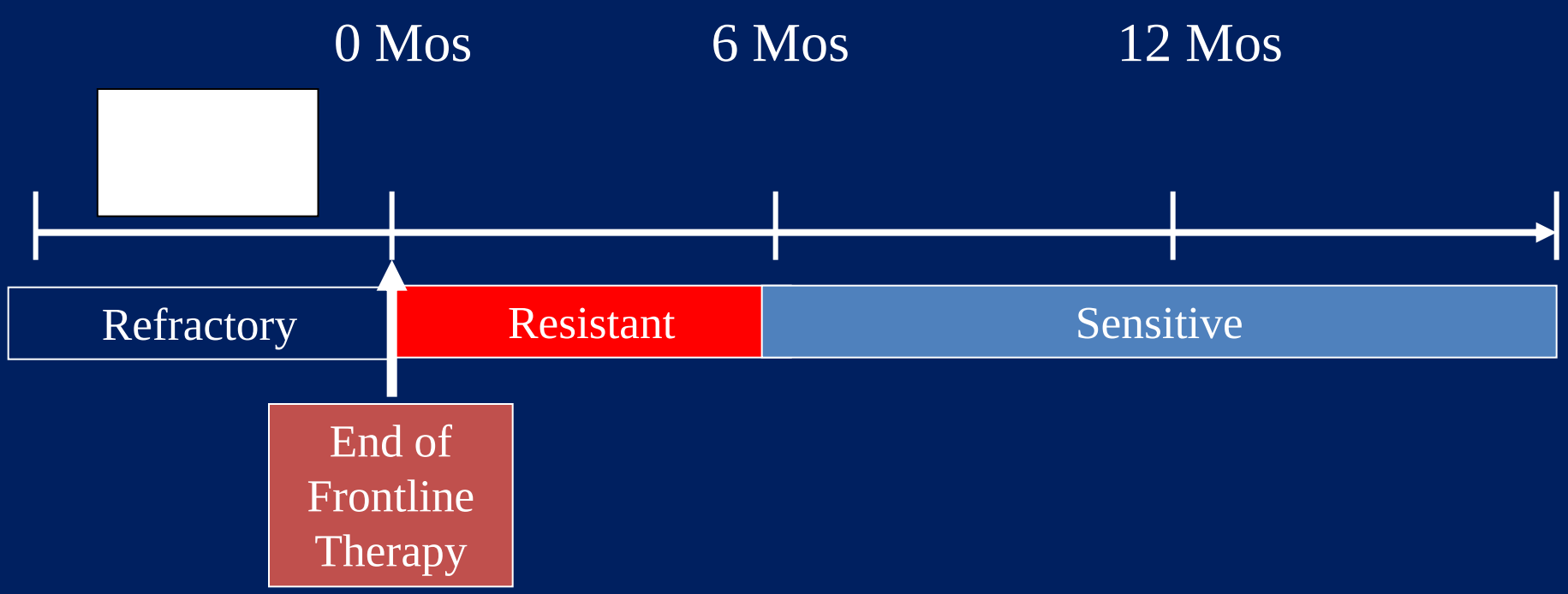
Pros

- Stay ahead of disease
- Improve survival?
- Prevent symptoms
- Maximize QoL
- “Active approach” to care
- Intuitive to do something
- Minimize patient anxiety
- Avoids patient “relocating”
- Shortens visit time

Cons

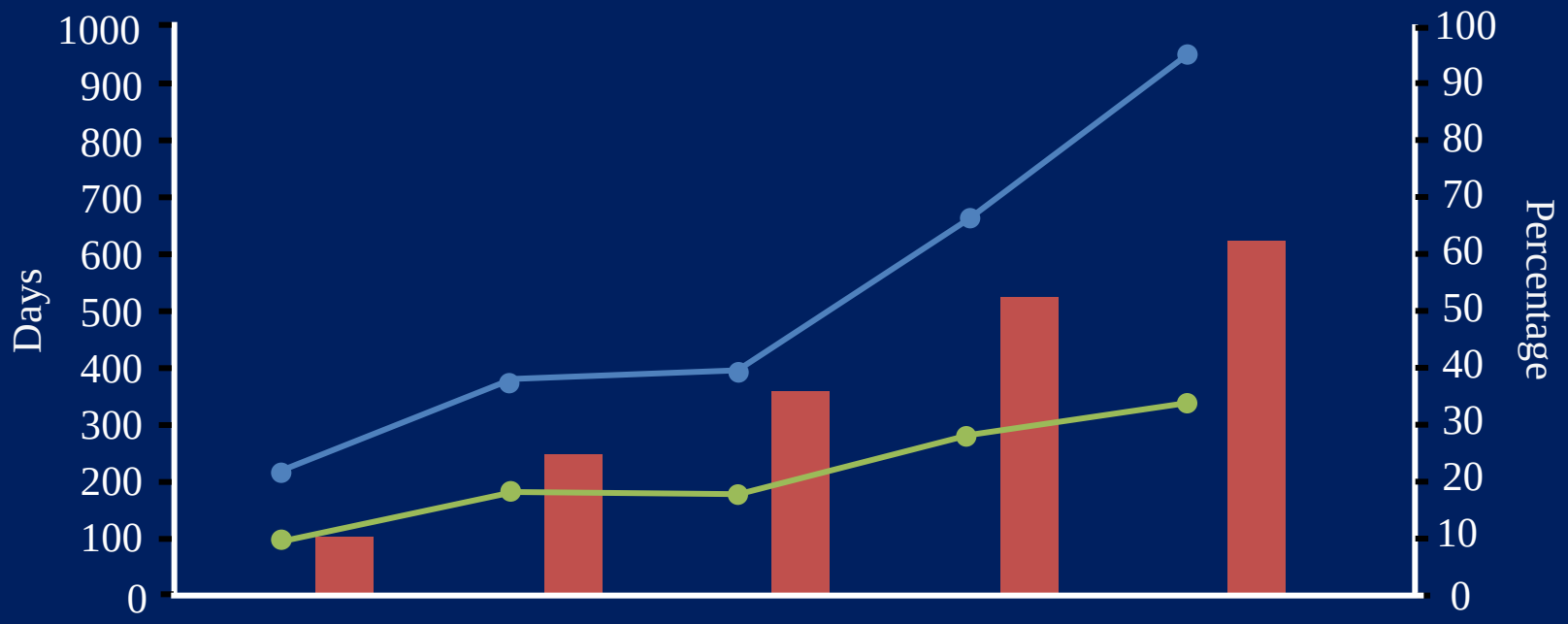
- Potential Rx of false positives
- No improvement in OS
- Exhaust treatment options
- Toxicity
- Impaired QoL
- Cost
- No ideal agent available
- May be homeopathic only

Platinum Sensitivity



Best Management Approaches for Patients With Platinum-Sensitive Recurrent Disease

Recurrent Ovarian Cancer: Effect of Platinum-Free Interval and Survival

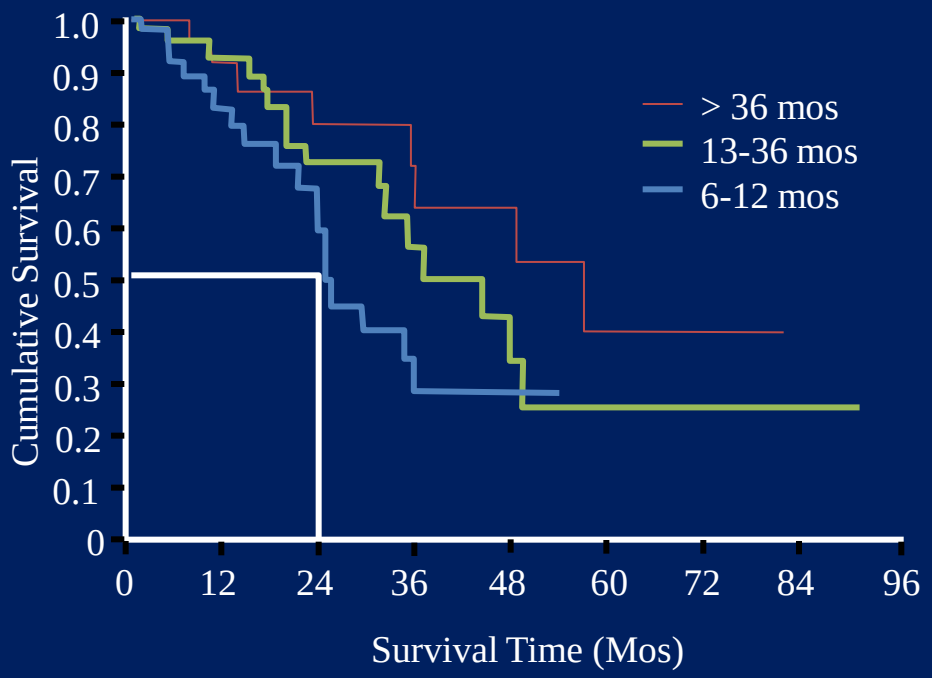


	0-3 Prog	0-3 Non-PD	3-12 Mos	12-18 Mos	18+ Mos
PFS, days	90	176	174	275	339
OS, days	217	375	375	657	957
Response, %	9	24	35	52	62

Pujade-Lauraine E, et al. ASCO 2002. Abstract 829.

Secondary Cytoreduction: Patients With Short PFIs Do Not Benefit?

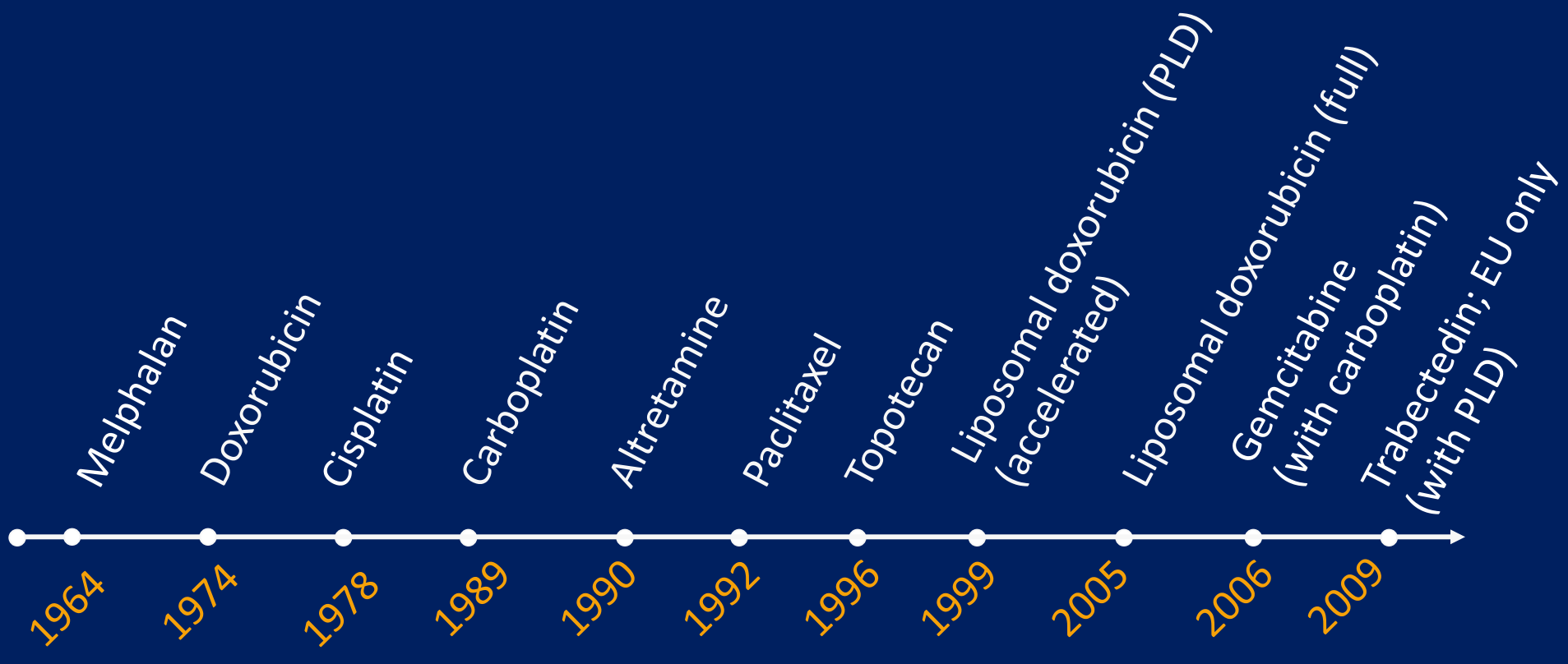
- Patients (N = 106)
  - Optimal (no visible tumor): 82%
  - All cisplatin based
  - PFI: 6 mos
- Time to second surgery: 16.8 mos (range: 6-109)



PFI = Platinum-free interval

Eisenkop SM, et al. Cancer. 2000;88:144-153.

FDA-Approved Drugs in Ovarian Cancer



Potential Advantages to Nonplatinum Agents in Intermediately Sensitive Disease

- Decreased toxicity
- Prolonged platinum-free interval
- Alternative mechanism of action

Positive Trials in Recurrent Ovarian Cancer

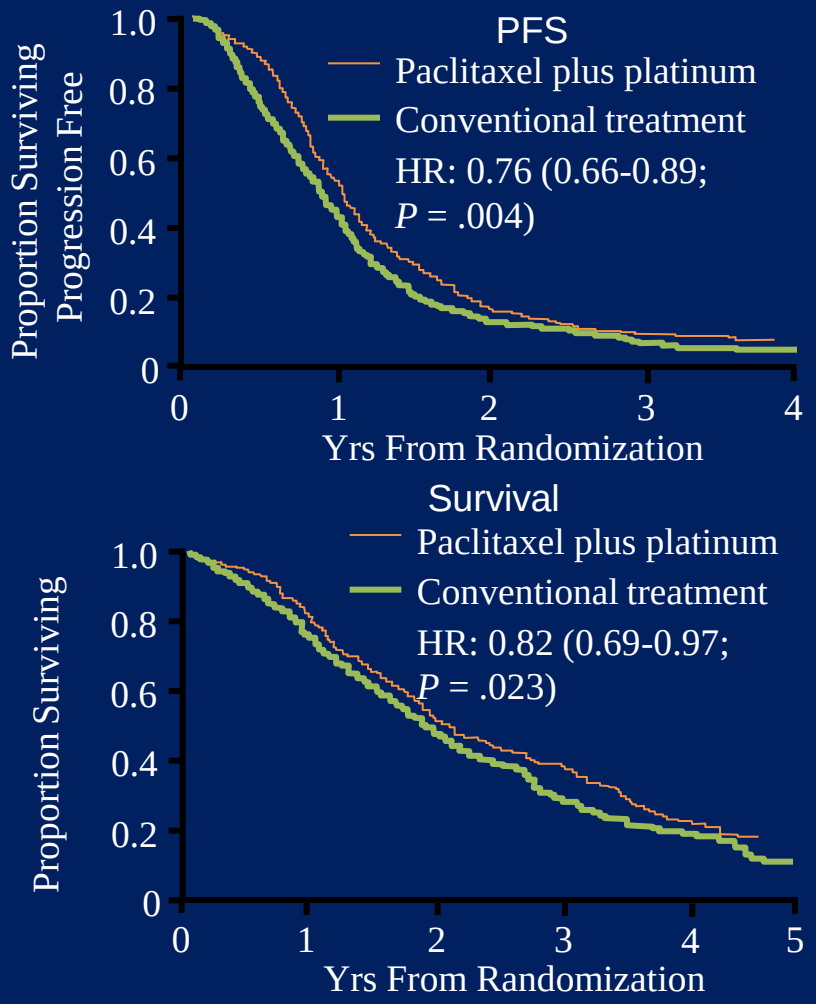
- Paclitaxel vs topotecan[1,2]
- Topotecan vs pegylated liposomal doxorubicin (PLD)[3,4]
- Platinum vs platinum + paclitaxel[5]
- Carboplatin vs carboplatin + gemcitabine[6]
- Carboplatin + PLD vs carboplatin + paclitaxel[7]
- PLD vs PLD + trabectedin[8]

1. ten Bokkel Huinink WW, et al. J Clin Oncol. 1997;15:2183-2193. 2. ten Bokkel Huinink WW, et al. Ann Oncol. 2004;15:100-103. 3. Gordon AN, et al J Clin Oncol. 2001;19:3312-3322. 4. Gordon AN, et al. Gynecol Oncol. 2004;95:1-8. 5. Parmar MK, et al. Lancet. 2003;361:2099-2106. 6. Pfisterer J, et al. J Clin Oncol. 2006;24:4699-4707. 7. Vasey P, et al. ECCO ESMO 2009. Abstract 18LBA. 8. Monk BJ, et al. ESMO 2008. Abstract LBA4

Platinum vs Platinum + Paclitaxel

- N = 802 (776 evaluable)

	Platinum	Platinum + Paclitaxel	*P* Value
Platinum sensitive, %	100	100	
Response rate, %	54	66	.06
Median PFS, mos	9	12	.0004
Median OS, mos	24	29	.02

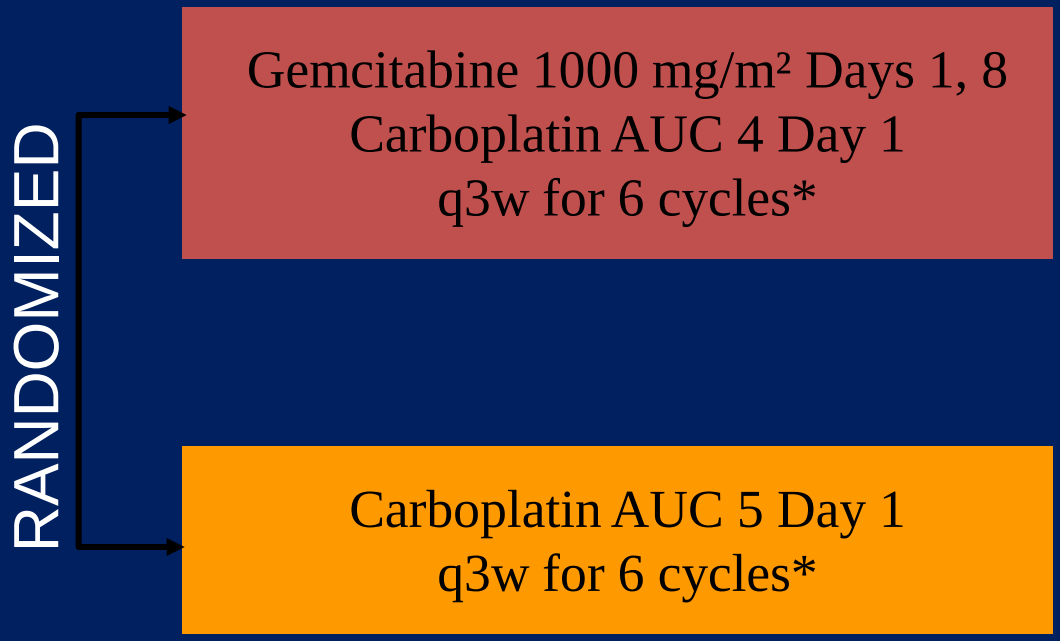


Parmar MK, et al. Lancet. 2003;361:2099-2106.

Phase III Trial of Carboplatin & Gemcitabine: Study Design

Stratified by:

- Platinum-free interval (6-12 or > 12 mos)
- Type of first-line platinum therapy (platinum/paclitaxel or other platinum therapy)
- Bidimensionally measurable disease (yes or no)



*Patients were treated for 6 cycles in the absence of progressive disease or unacceptable toxicity.

At investigator discretion, benefiting patients could receive a maximum of 10 cycles.

Pfisterer J, et al. J Clin Oncol. 2006;24:4699-4707.

Phase III Registration Trial Carbo/Gem: Prespecified Subgroup Analysis for PFS

Median PFS	Gemcitabine/Carboplatin, Mos	Carboplatin, Mos
Progression-free interval (6-12 mos)	7.9	5.2
Progression-free interval (> 12 mos)	9.7	6.7
Previous platinum and paclitaxel	9.7	5.9
Previous platinum (no paclitaxel)	7.6	5.7

ASCO Virtual Meeting 2003; Abstract and presentation 5005, slides 13-16.

PLD + Carbo in Ovarian Cancer Pts Who Recur Within 6-12 Mos: Phase II Study

- PLD 30 mg/m^2 followed by carboplatin AUC 5 mg/mL/min every 4 wks
- N = 54
- 75% received at least 6 cycles
- RECIST RR: 46% (4% CR and 42% PR)
  - Additional 33% experiencing disease stabilization > 6 mos
- CA-125 RR: 66% (28% CR and 38% PR)
  - Additional 18% experiencing disease stabilization > 6 mos
- Median TTP: 10.0 mos (range: 1.5-25.0)
- Median OS: 19.1 mos (range: 2.2-38.9)
- Most frequent adverse effects were neutropenia, thrombocytopenia, and constipation

Power P, et al. Gynecol Oncol. 2009;114:410-414.

CALYPSO Study Schema

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

Ovarian cancer in relapse > 6 mos after first- or second-line platinum + taxane chemotherapy

RANDOMIZE

Experimental arm: CD
PLD 30 mg/m^2 IV Day 1
Carboplatin AUC 5 Day 1

q28 days x 6 courses*

Control arm: CP
Paclitaxel 175 mg/m^2 IV Day 1
Carboplatin AUC 5 Day 1

q21 days x 6 courses*

Stratification

- Center
- Measureable disease (yes vs no)
- Therapy-free interval (6-12 mos vs > 12 mos)

*Or progression in patients with SD or PR.

Accrual

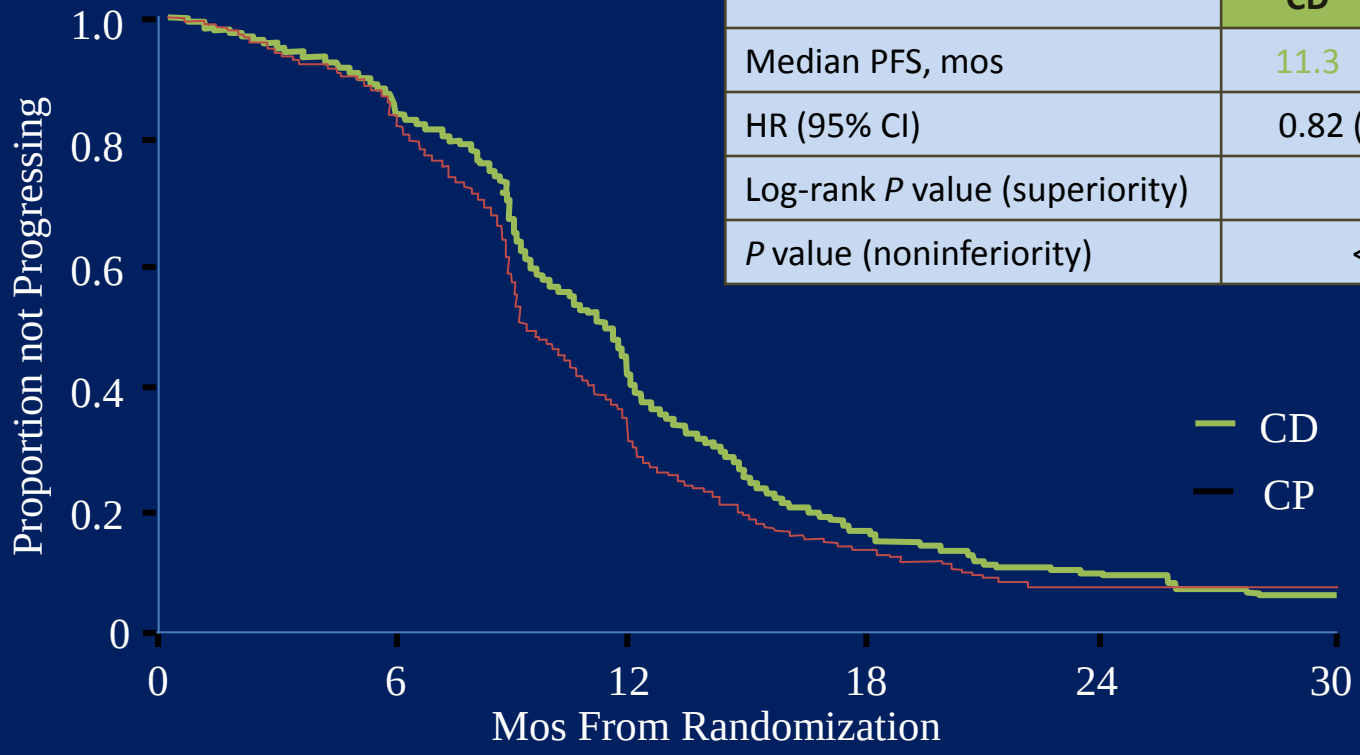
- AGO-OVAR (Germany), GINECO (France, Switzerland, Turkey, Saudi Arabia), NSGO (Denmark, Finland, Norway, Sweden), NCIC-CTC (Canada), ANZGOG (Australia, New Zealand), AGO (Austria), EORTC (Netherlands, Belgium, Spain), MITO (Italy), MANGO (Italy)

	Treatment		Total
Therapy-Free Interval	**CD, n (%)**	**CP, n (%)**	
6-12 mos	161 (35)	183 (36)	344 (35)
> 12 mos	305 (65)	326 (64)	631 (65)

Vasey P, et al. ECCO ESMO 2009. Abstract 18LBA.

Progression-Free Survival (ITT): Primary Endpoint

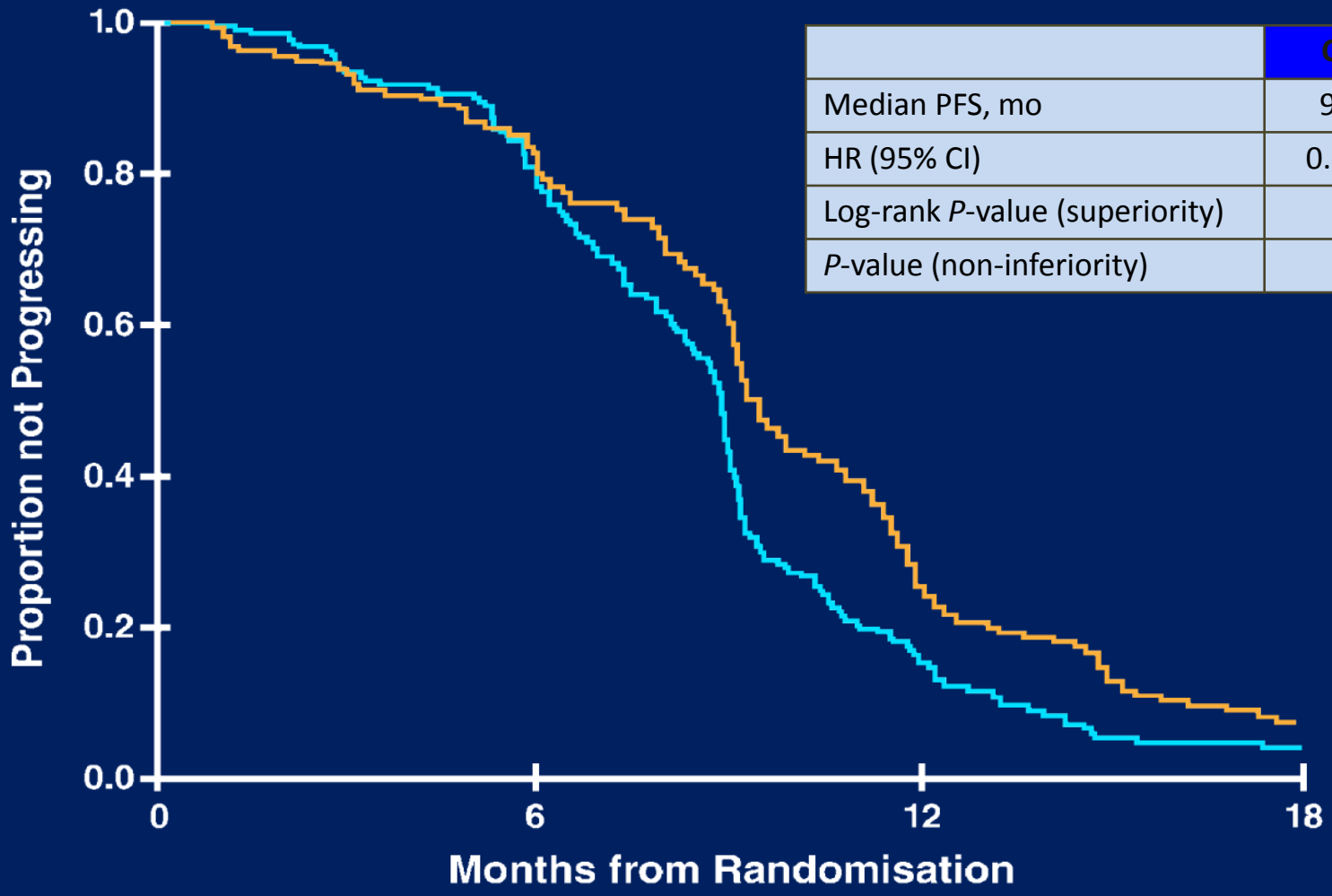
	CD	CP
Median PFS, mos	11.3	9.4
HR (95% CI)	0.82 (0.72-0.94)	
Log-rank *P* value (superiority)	.005	
P value (noninferiority)	< .001	



Patients at Risk, n						
CD	467	397	188	60	20	4
CP	509	405	152	45	10	2

Vasey P, et al. ECCO ESMO 2009. Abstract 18LBA. Reprinted with permission from the author.

PFS 6-12 Month Segment



	CD	CP
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 ESMO 2009. Abstract 18LBA. Reprinted with permission from the author.

Platinum-Resistant Disease: Practice Guidelines

- Pts with PD, SD, or persistent disease receiving primary chemotherapy should receive
  - Supportive care
  - Recurrence therapy
  - Referral to a clinical trial
- Pts achieving CR and relapse within 6 mos following chemotherapy OR pts with stage II-IV disease with PR should receive
  - Observation
  - Recurrence therapy (such as with non-platinum-based single agent therapy)
  - Referral to a clinical trial

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

Platinum-Resistant Disease

Single-agent (non-platinum based)

- PLD
- Docetaxel
- Gemcitabine
- Etoposide (oral)
- Pemetrexed
- Topotecan
- Paclitaxel (wkly)

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

Summary of Phase III Single-Agent Trials: Recurrent Ovarian Cancer

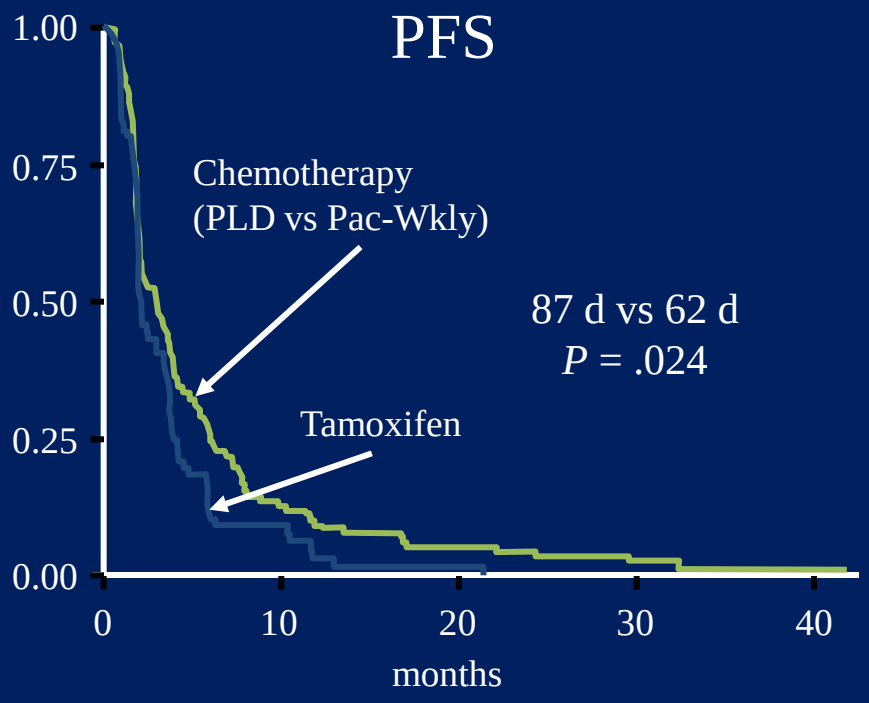
Drug A	Drug B	N	TTP (wks)	*P*	OS (wks)	*P*	Comment
Topotecan	Paclitaxel	226	23 vs 14	NS	61 vs 43	NS	50% Cross-over
Paclitaxel (bolus)	Paclitaxel (weekly)	208	38 vs 26	NS	34 vs 59	NS	Less toxicity w/ weekly
Oxaliplatin	Paclitaxel	86	12 vs 14	NS	42 vs 37	NS	74% platinum resistant
PLD	Topotecan	481	16 vs 17	NS	60 vs 57	NS	54% platinum resistant; OS benefit in platinum-sensitive subgroup
PLD	Paclitaxel	214	22 vs 22	NS	46 vs 56	NS	All pts taxane-naive
Topotecan	Treosulfan	357	22 vs 12	.001	56 vs 48	.02	2^{nd} – 3^{rd} line therapy
PLD	Gemcitabine	195	16 vs 13	NS	59 vs 55	NS	
PLD	Gemcitabine	153	16 vs 20	NS	55 vs 50	NS	56% platinum resistant
PLD or Topotecan	Canfosfamide	461	19 vs 9	< .01	59 vs 37 (PLD: 62 vs Topo: 47)	< .0001	ASSIST-1 trial All 3^{rd} line

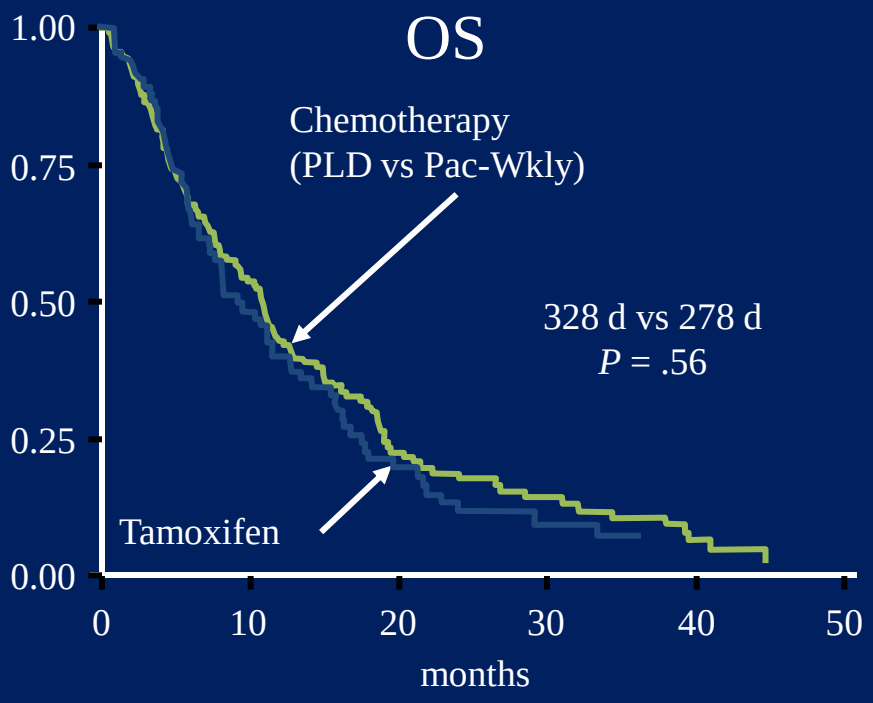
Taxanes in Platinum Resistant Disease GOG 126-L

Drug	Study	N	RR, %	PFS (mos)	OS (mos)
Docetaxel	126-L	58	22	2.1	12.7
Paclitaxel wkly	126-N	48	21	3.6	NS
nab-paclitaxel	126-R	51	23	4.5	17.4
Paclitaxel poliglumex	186-C	49	16	2.8	15.4

Chemotherapy vs Hormones

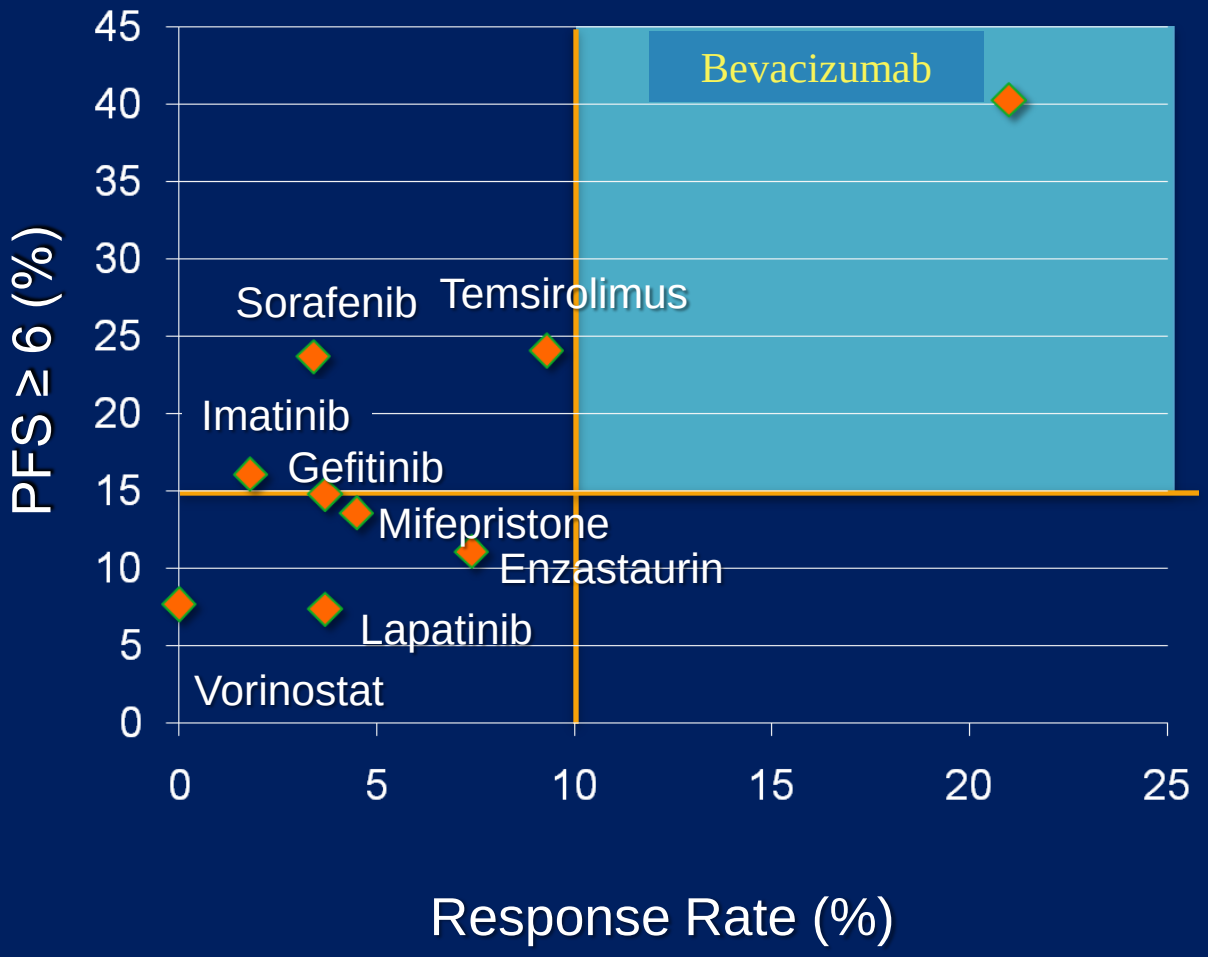
N = 241 platinum/taxane-resistant





Kristensen GB, et al. IGCS 2008. Abstract 2008_1175.

Targeted Therapies



Phase II Studies of Bevacizumab in Recurrent Ovarian Cancer

Measure, %	Cannistra et al[1] (N = 44)	Garcia et al[2] (N = 70)	Burger et al[3] (N = 62)
Previous regimens			
▪ 1		100%	34%
▪ 2	52%		66%
▪ 3	48%		
Response rate			
▪ CR	0%	0%	3%
▪ PR	16%	24%	18%
Gastrointestinal perforations	11%	6%	0%
Arterial thrombosis	7%	4%	0%
Bevacizumab-related deaths	7%	4%	0%

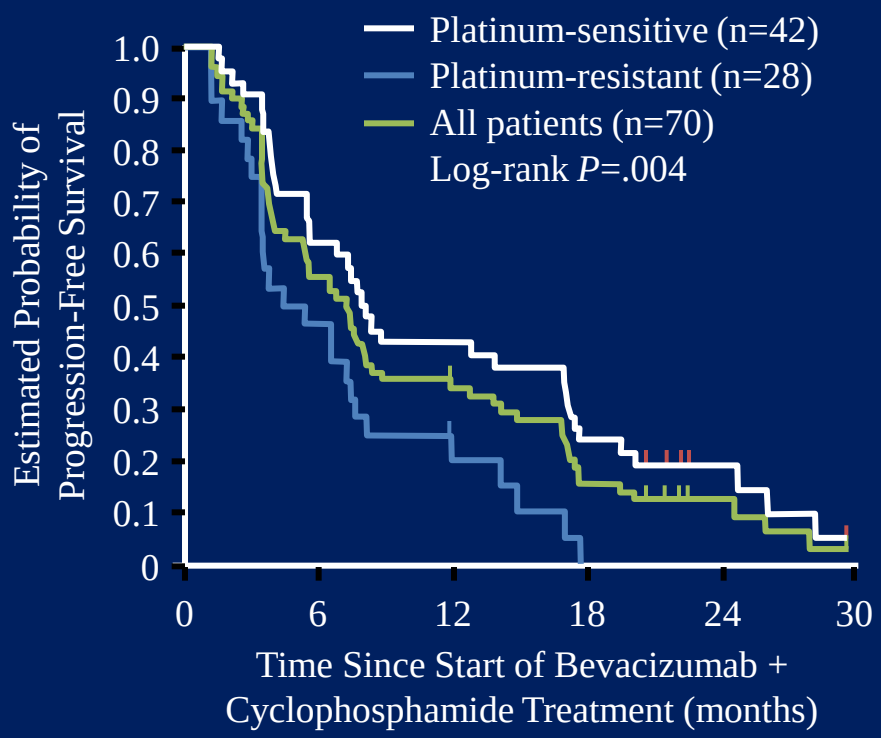
1. Cannistra SA, et al. J Clin Oncol. 2007;25:5180-5186.
2. Garcia AA, et al. J Clin Oncol. 2008;26:76-82.
3. Burger RA, et al. J Clin Oncol. 2007;25:5165-5171.

Platinum-Sensitivity and Bevacizumab

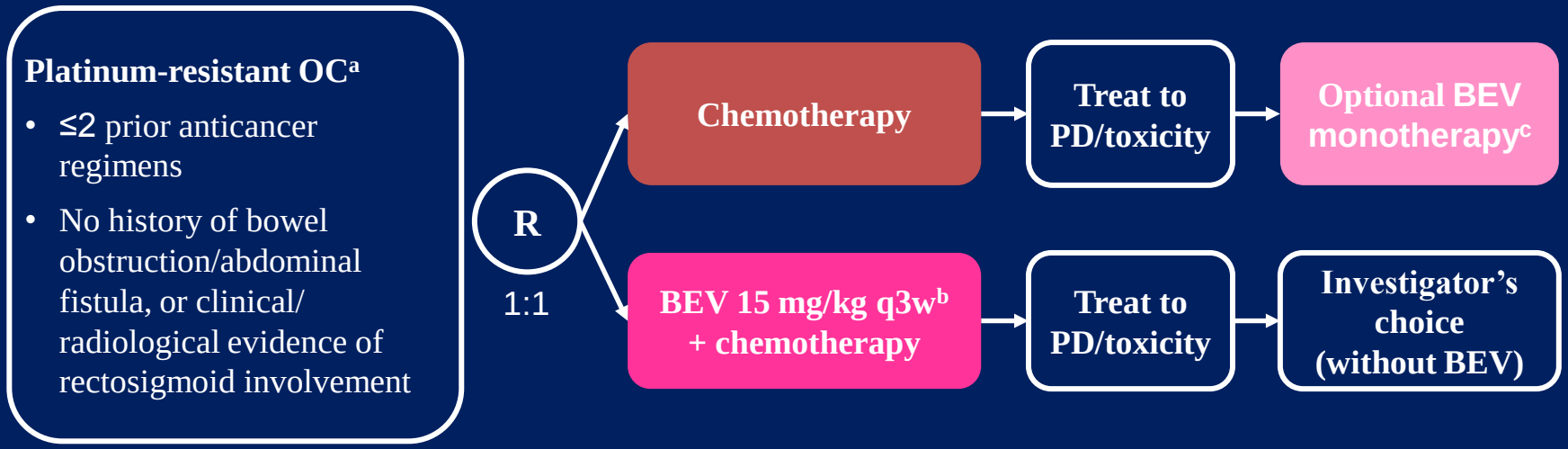
GOG-170D (Burger et al.)

Parameter	Wald *P*	HR (95% CI)
GOG PS > 0 vs 0	0.25	1.49 (0.76-2.9)
Plat-S Y vs N	0.47	0.80 (0.44-1.46)
Age	0.91	1.0 (0.98-1.02)
Prior chemo 2 vs 1	0.12	0.62 (0.33-1.14)

(Garcia, et al.)



AURELIA trial design



Stratification factors:

- Chemotherapy selected
- Prior anti-angiogenic therapy
- Treatment-free interval (<3 vs 3–6 months from previous platinum to subsequent PD)

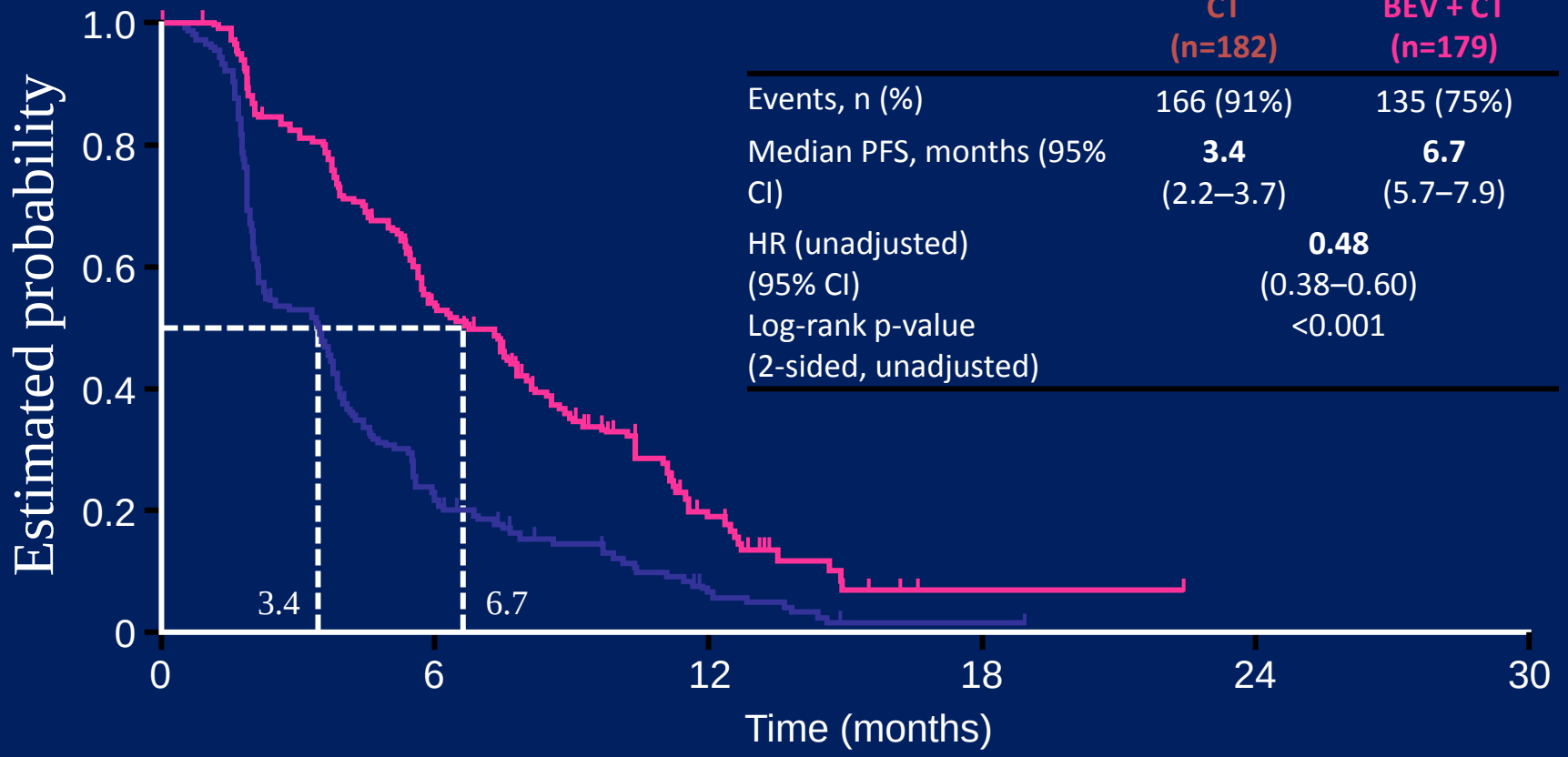
Chemotherapy options (investigator's choice):

- 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

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer; [b]Or 10 mg/kg q2w; [c]15 mg/kg q3w, permitted on clear evidence of progression

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	

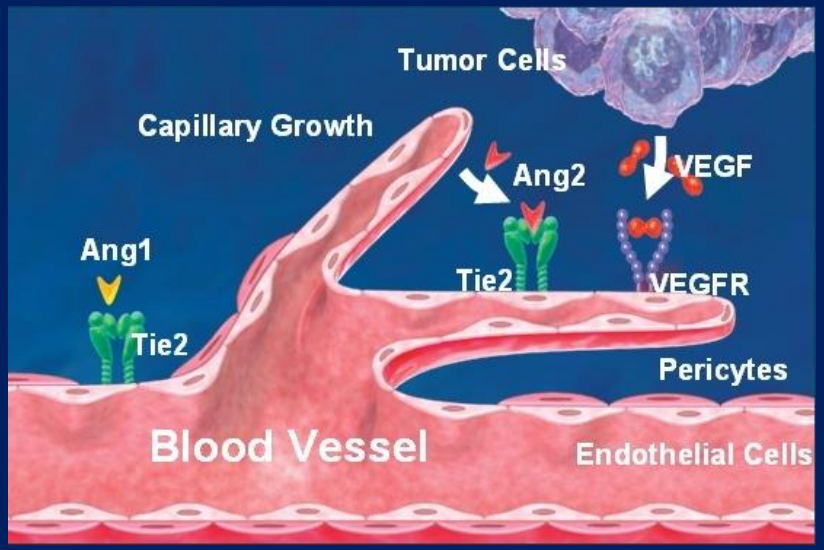
No. at risk:

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

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

The Angiopoietin Axis

- Angiogenesis is a complex process that may be regulated by a number of different factors (eg, VEGF and angiopoietins)[1]
- Angiopoietins interact with the Tie2 receptor, which mediates vascular remodeling[1,2]

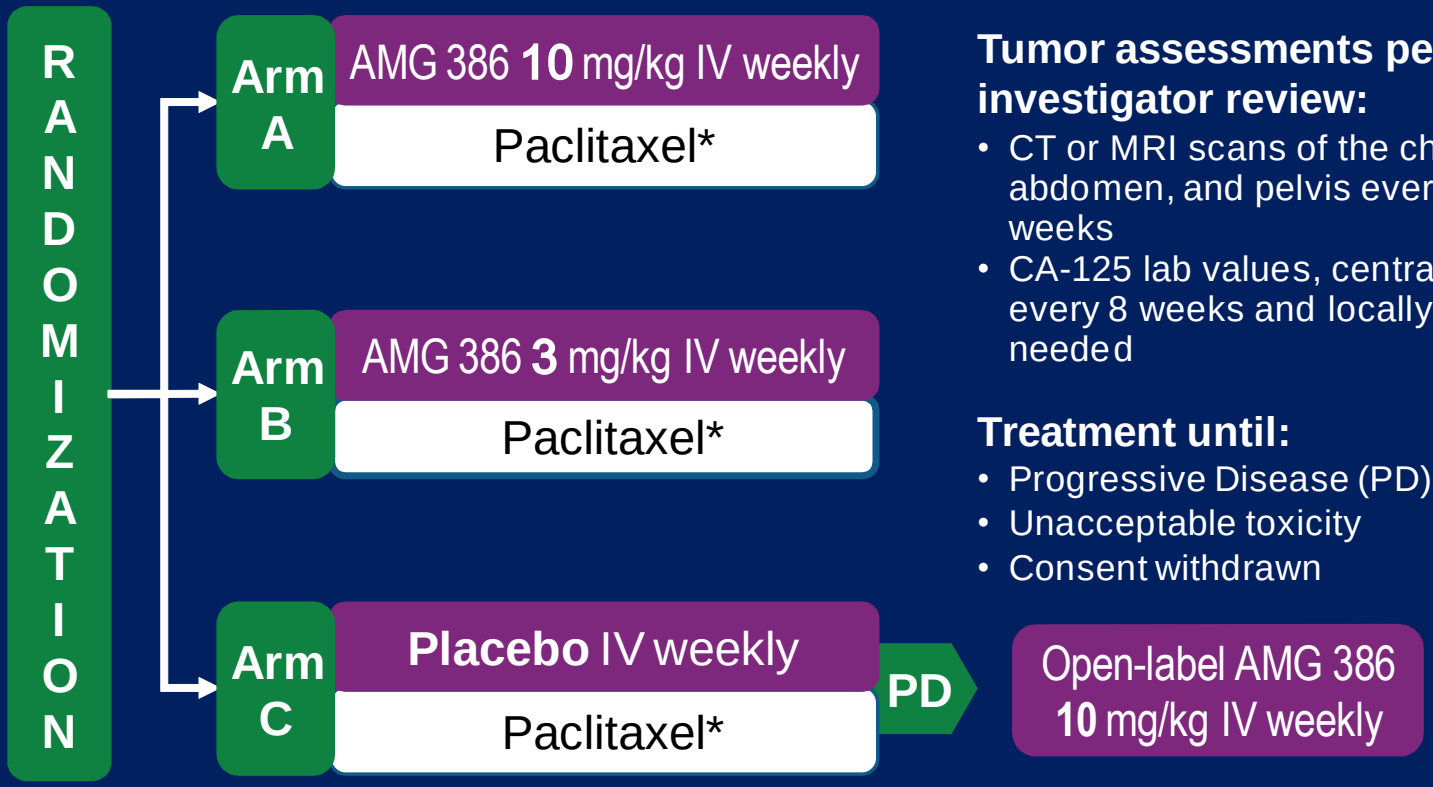


  - Ang1 promotes vessel stabilization by increasing endothelial junctions and pericyte coverage[3,4]
  - Ang2 blocks Ang1's blood vessel stabilizing action and increases angiogenesis and vascularity in tumors[4,5]
  - Ang2 is upregulated in many ovarian cancers[6]

1. Papapetropoulos A, et al. *J Biol Chem*. 2000;275:9102-9105.
2. Oliner J, et al. *Cancer Cell*. 2004;6:507-516.
3. Machein MR, et al. *Am J Pathol*. 2004;165:1557-1570.
4. Falcon BL, et al. *Am J Pathol*. 2009;175:2159-2170.
5. Scharpfenecker M, et al. *J Cell Sci*. 2005;118:771-780.
6. Zhang L, et al. *Cancer Res*. 2003;63:3403-3412

Methods

Study 20060342 Schema



Tumor assessments per investigator review:

- CT or MRI scans of the chest, abdomen, and pelvis every 8 weeks
- CA-125 lab values, centrally every 8 weeks and locally as needed

Treatment until:

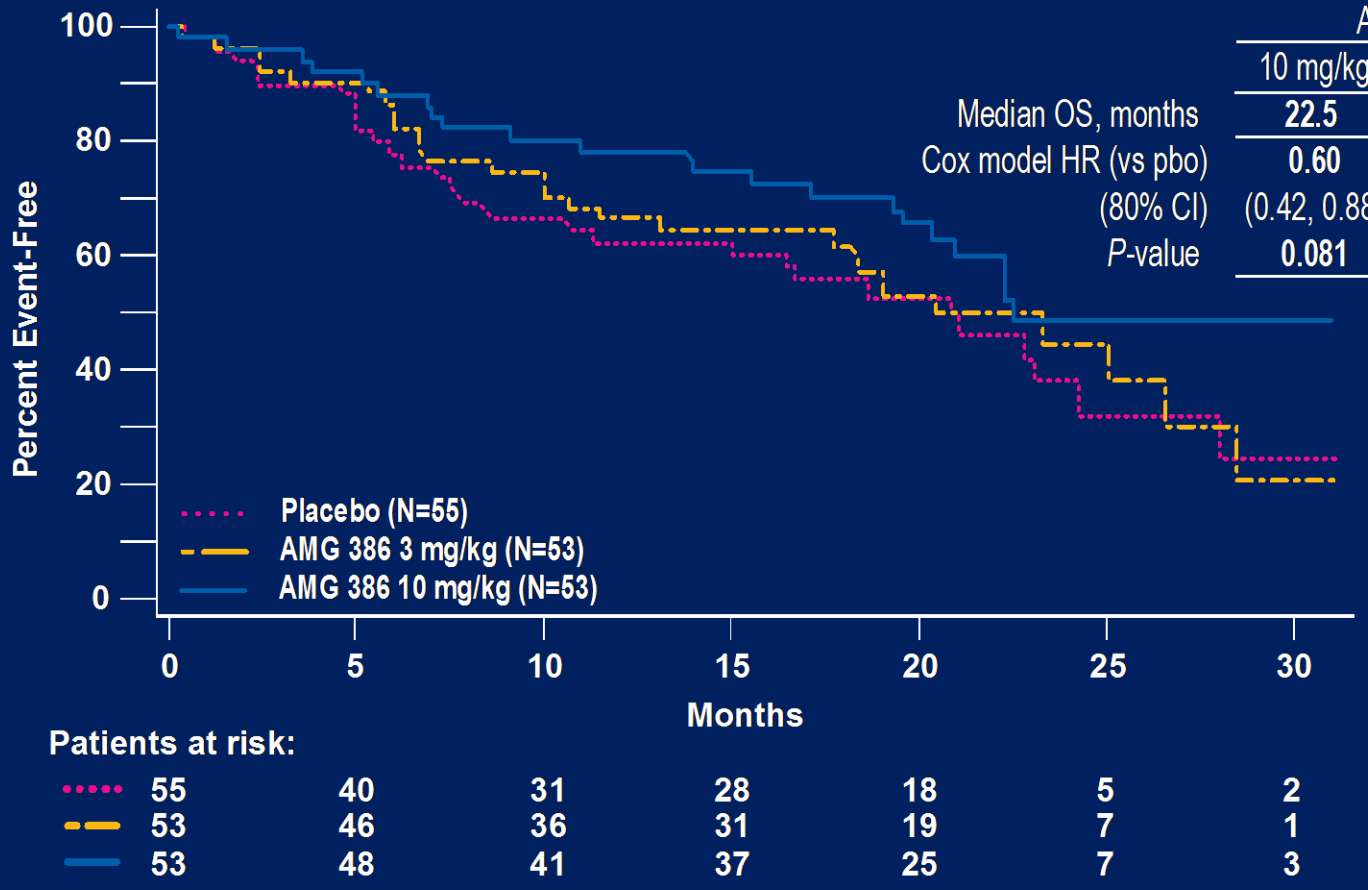
- Progressive Disease (PD)
- Unacceptable toxicity
- Consent withdrawn

*Paclitaxel 80 mg/m^2 IV weekly, 3 weeks on/1 week off

This study was conducted at 38 sites in 5 countries; 161 patients were randomized

Results

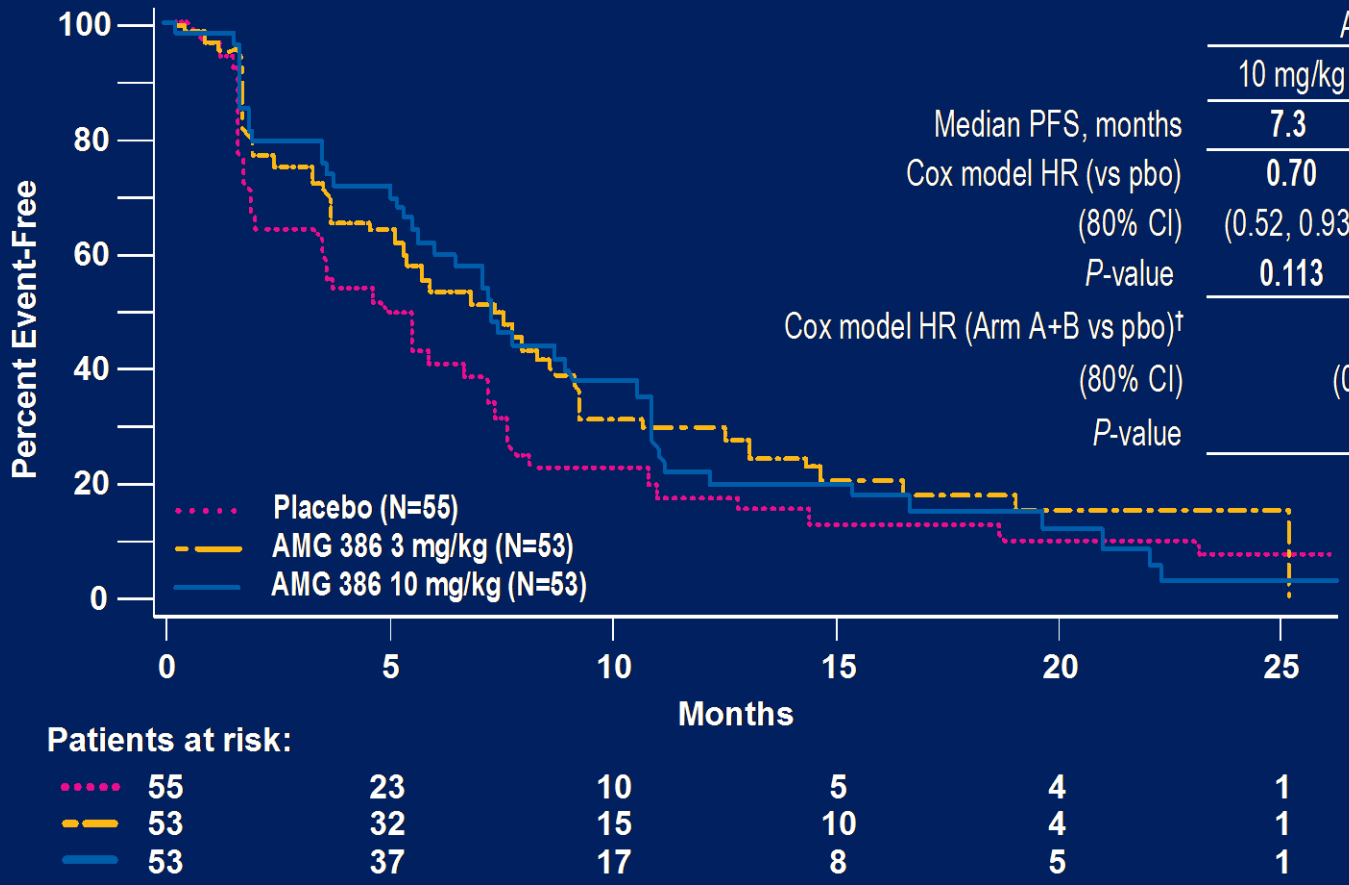
Overall Survival



	AMG 386		
	10 mg/kg	3 mg/kg	Placebo
Median OS, months	**22.5**	**20.4**	**20.9**
Cox model HR (vs pbo)	**0.60**	**0.77**	
(80% CI)	(0.42, 0.88)	(0.54, 1.09)	
P-value	**0.081**	**0.330**	

Results

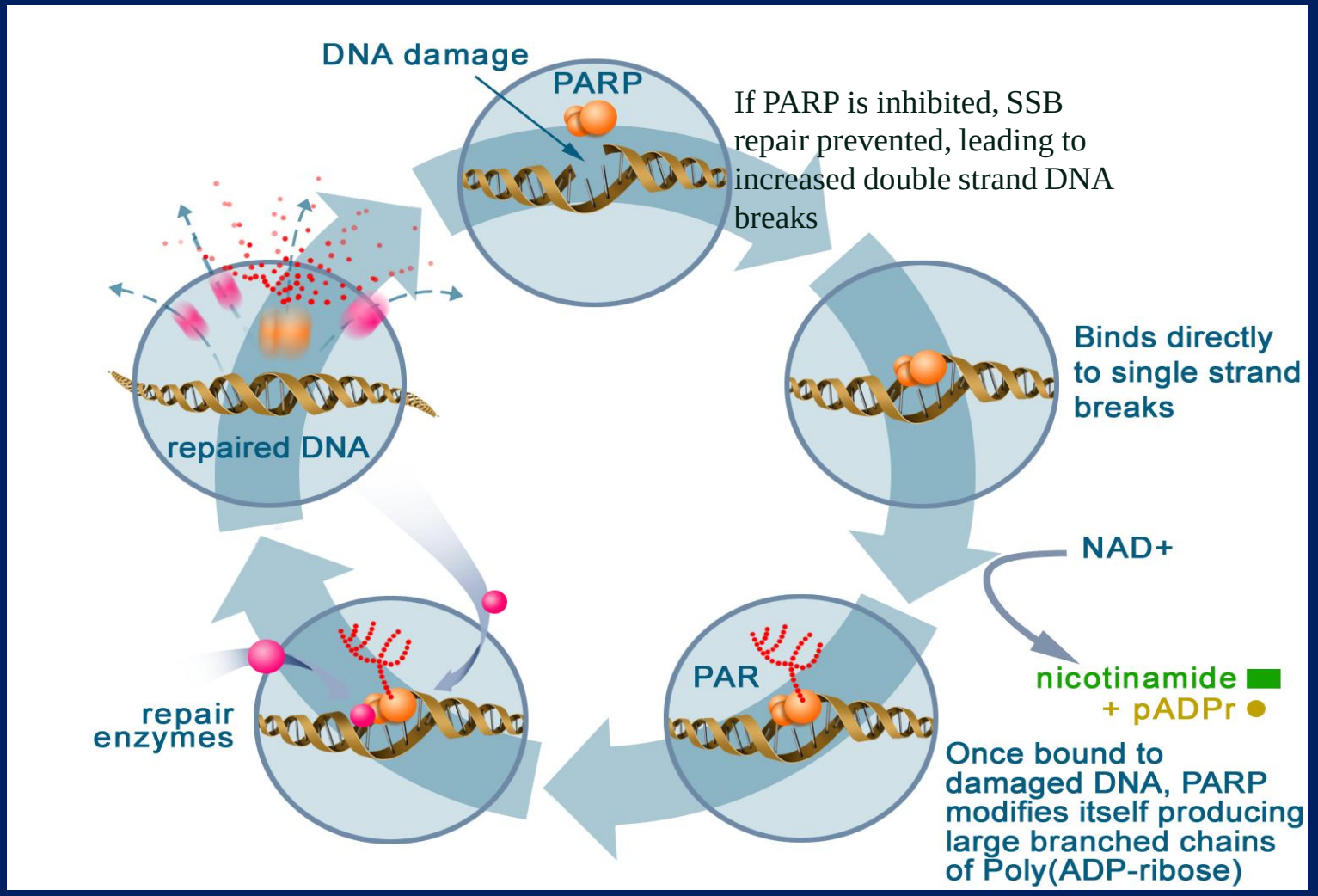
*Progression-Free Survival**



	AMG 386		
	10 mg/kg	3 mg/kg	Placebo
Median PFS, months	7.3	7.4	5.0
Cox model HR (vs pbo)	0.70	0.57	
(80% CI)	(0.52, 0.93)	(0.42, 0.77)	
P-value	0.113	0.016	
Cox model HR (Arm A+B vs pbo)†	0.64		
(80% CI)	(0.50, 0.82)		
P-value	0.022		

*PFS is defined as time from randomization to disease progression per RECIST, CA-125 (GCIG criteria), clinical progression, or death. †Primary endpoint.

Poly (ADP-Ribose) Polymerase



Phase II randomized placebo-controlled study of olaparib (AZD2281) in patients with platinum-sensitive relapsed serous ovarian cancer

Jonathan Ledermann on behalf of the Study 19 investigators

UCL Cancer Institute, University College London

This study was sponsored by AstraZeneca

Study 19 – Aim and design

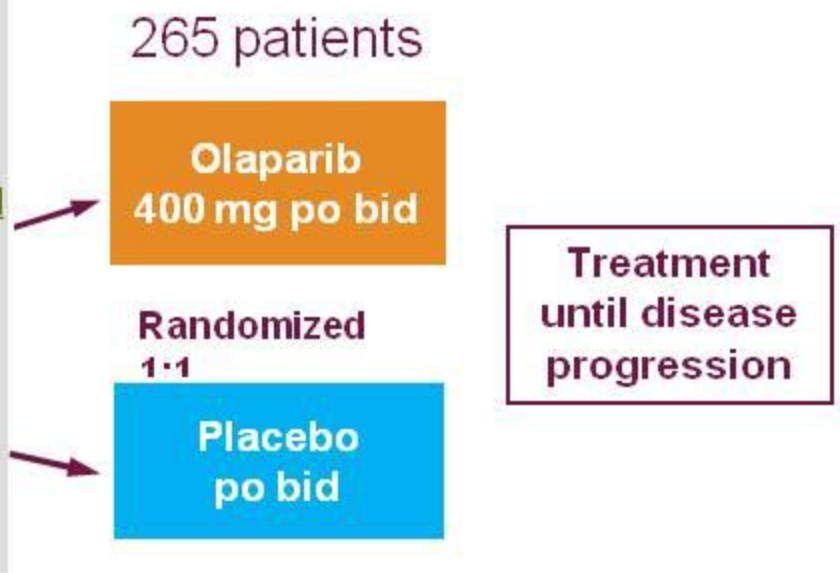
To assess the efficacy of the potent oral PARP inhibitor olaparib as a maintenance treatment in patients with platinum-sensitive high-grade serous ovarian cancer

Randomized, double-blind, placebo-controlled Phase II study

Multinational study; 82 sites in 16 countries

Patient eligibility

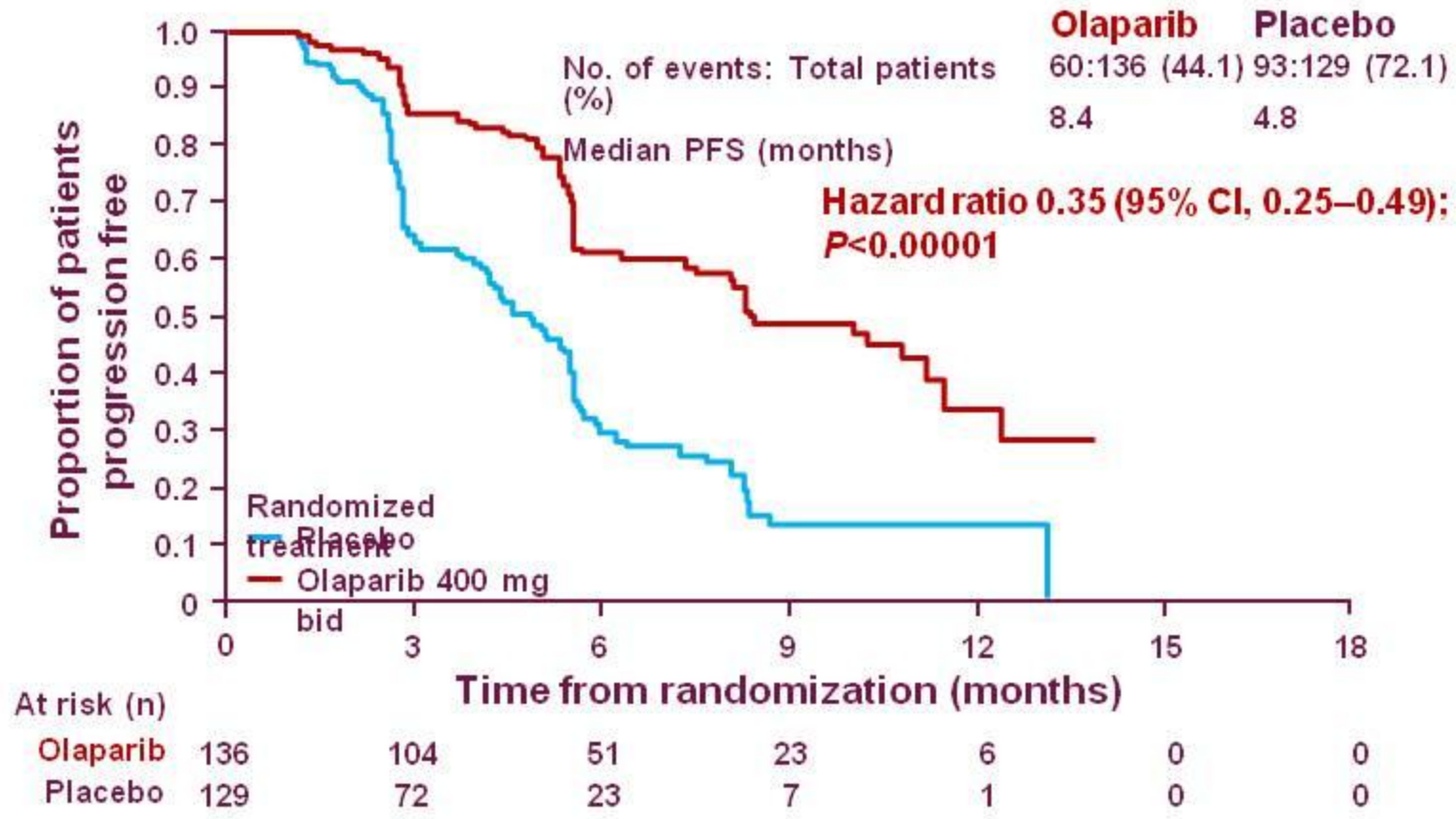
- **Platinum-sensitive high-grade serous ovarian cancer**
- **≥2 previous platinum regimens**
- **Last chemotherapy: platinum-based with a maintained response**
- **Stable CA125 at trial entry**
- **Randomization stratification factors:**
  - **Time to disease progression on penultimate platinum therapy**
  - **Objective response to last platinum therapy**
  - **Ethnic descent**



Ledermann J *et al. N Engl J Med* 2012;Mar 27 (Epub ahead of print)

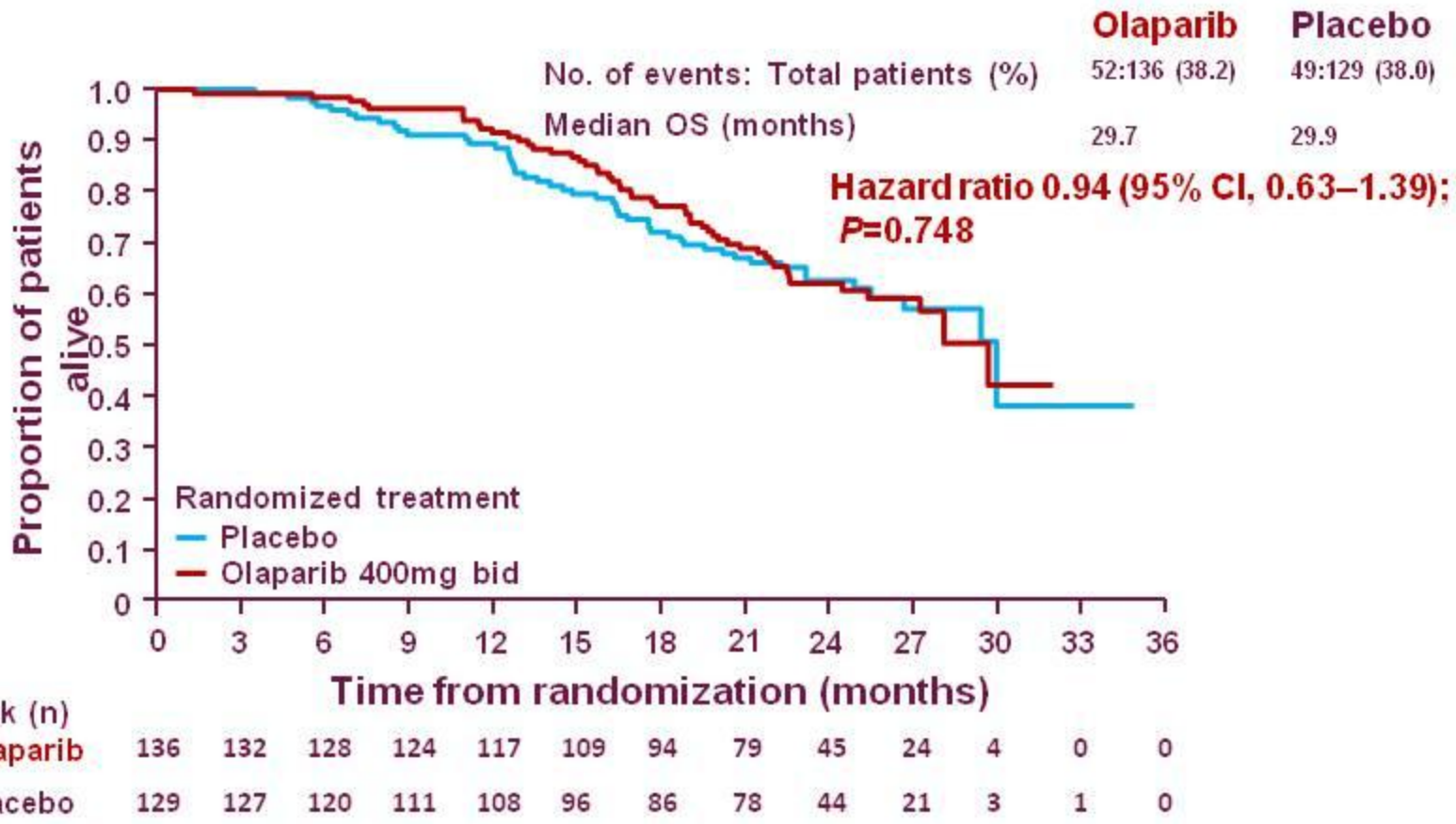
ClinicalTrials.gov NCT00753545

Progression-free survival



Ledermann J *et al. N Engl J Med* 2012;Mar 27 (Epub ahead of print)

Overall survival: interim analysis*



Ledermann J *et al. N Engl J Med* 2012;Mar 27 (Epub ahead of print)

*Performed at 38% maturity

Secondary endpoints

- Overall survival
  - Further analyses are ongoing to explore the reasons for the observed interim results
  - A final analysis will be performed at 60% maturity
- Objective response rate by RECIST
  - 7/57 (12.3%) PR in olaparib 400 mg bid group
  - 2/48 (4.2%) PR placebo group
- Quality of Life
  - No significant improvement or deterioration in Health-related Quality of Life Scales

Ledermann J *et al. N Engl J Med* 2012;Mar 27 (Epub ahead of print)

Conclusions

- Significant PFS benefit following maintenance treatment with a PARP inhibitor for platinum-sensitive relapsed serous ovarian cancer
  - Median PFS improved by 3.6 months compared with placebo, following completion of chemotherapy
  - No overall survival benefit observed at a subsequent interim analysis
- Well tolerated, no significant difference in improvement rates or time to worsening of HRQoL measures
- 50% of olaparib and 16% of placebo patients were still on treatment at the time of the PFS analysis
- Future development directions?

Ledermann J *et al. N Engl J Med* 2012;Mar 27 (Epub ahead of print)

Study aim and design

- To assess the efficacy of oral olaparib as a maintenance treatment in patients with platinum-sensitive high-grade serous ovarian cancer
- Randomized, double-blind, placebo-controlled Phase II study
- Multinational study; 82 sites in 16 countries

Patient eligibility:

- Platinum-sensitive high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy: platinum-based with a maintained response
- Stable CA125 at trial entry
- Randomization stratification factors:
  - Time to disease progression on penultimate platinum therapy
  - Objective response to last platinum therapy
  - Ethnic descent

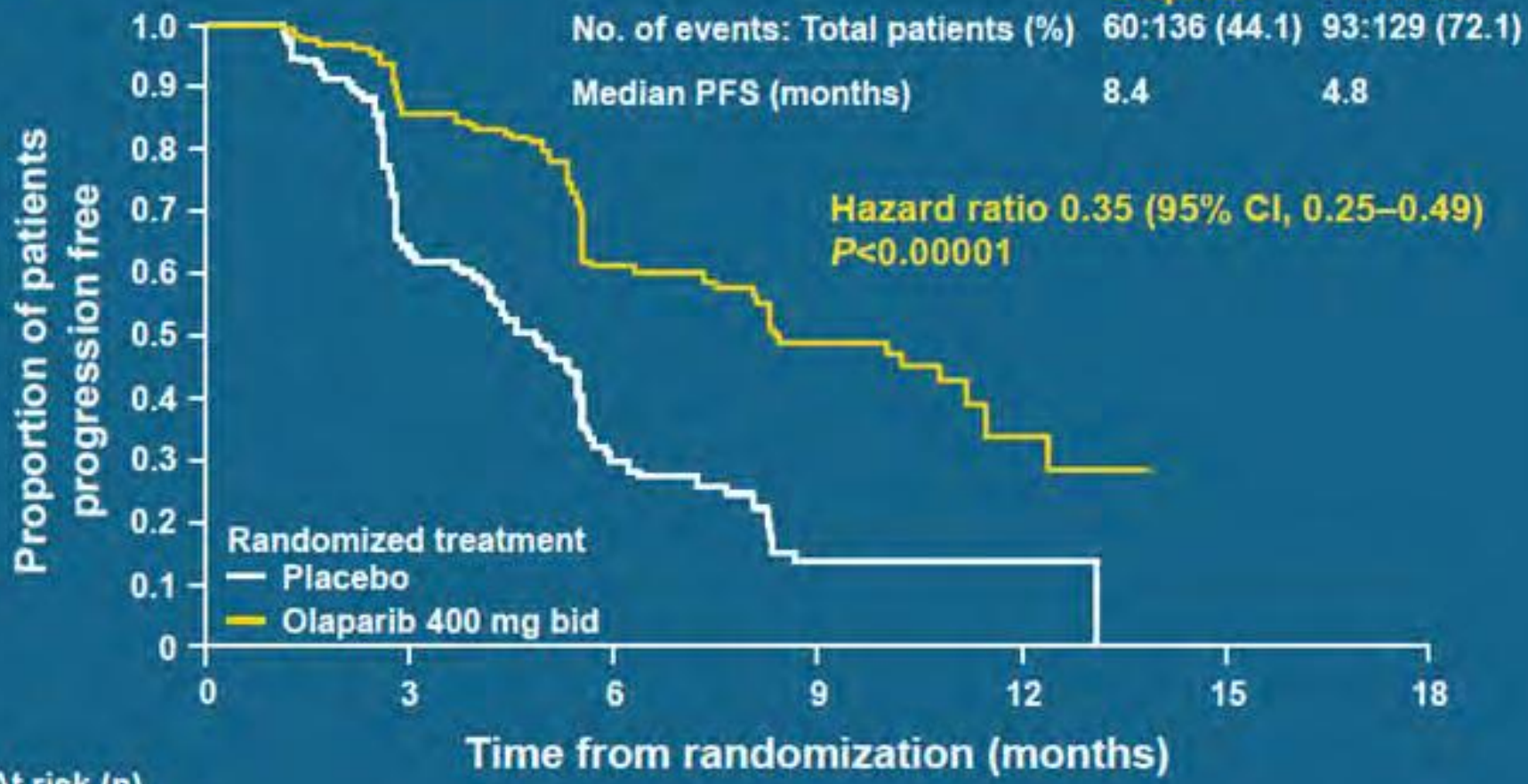
Olaparib
400 mg po bid

Randomized 1:1

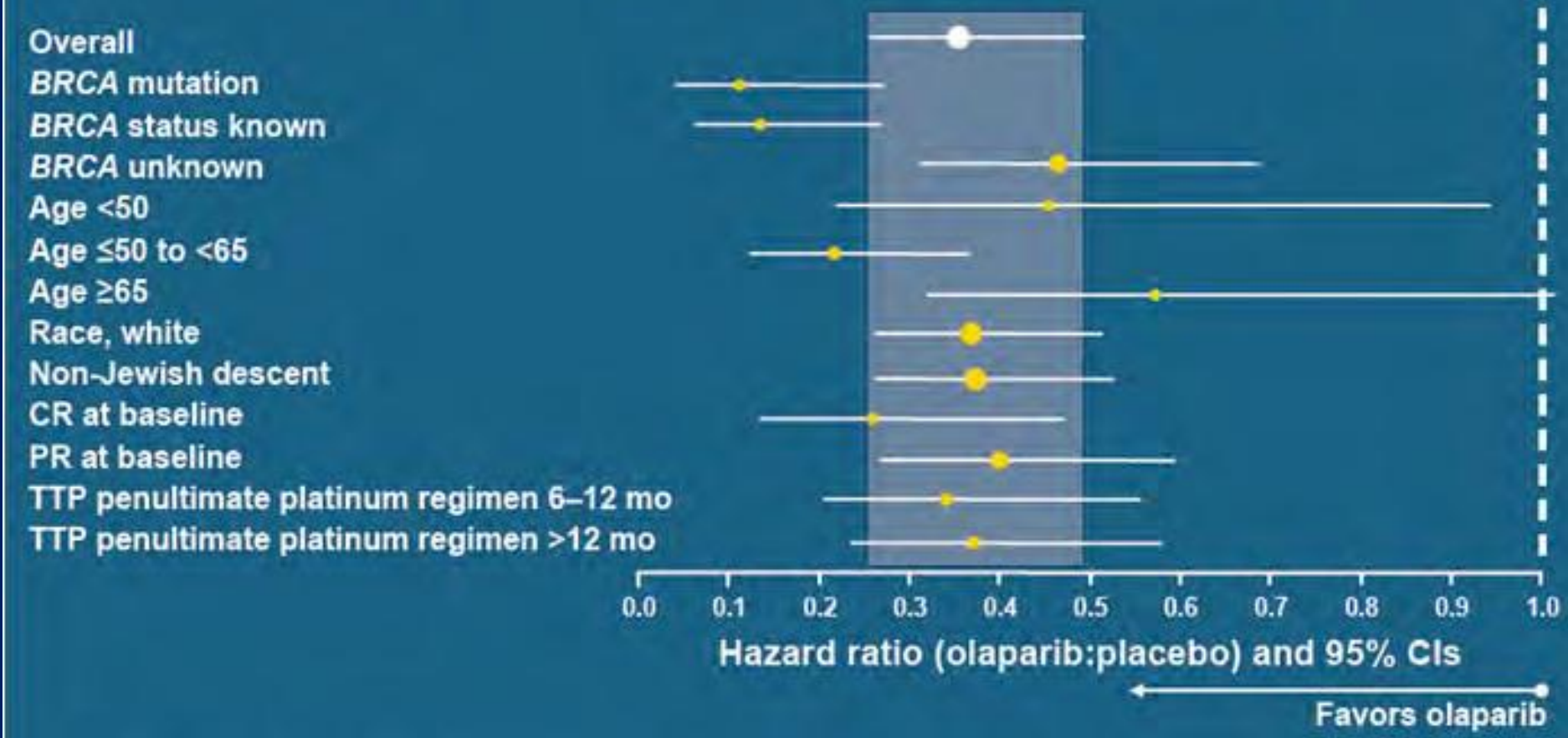
Placebo
po bid

Treatment until disease progression

Progression-free survival



Preplanned subgroup analysis of PFS



Global interaction test showed no evidence of inconsistency across the subgroups (P=0.282)

Size of circle is proportional to number of events; grey band represents 95% confidence intervals (CIs) in overall population

Investigational Agents

Biologics

- AMG-386 (Tie2)
- Pazopanib
- BIBF-1120
- IMC-1121B
- Fosbretabulin
- IMC-3G3
- IGF-1R inhibitors
- Rapalogs
- PARPi

Chemotherapy and Others

- Epothilones
  - Ixabepilone
- BMP-1350 (karenitecan)
- NKTR-102
- EC-145
- Farletuzumab

The Future PI3-kinase: a hot topic in cancer research