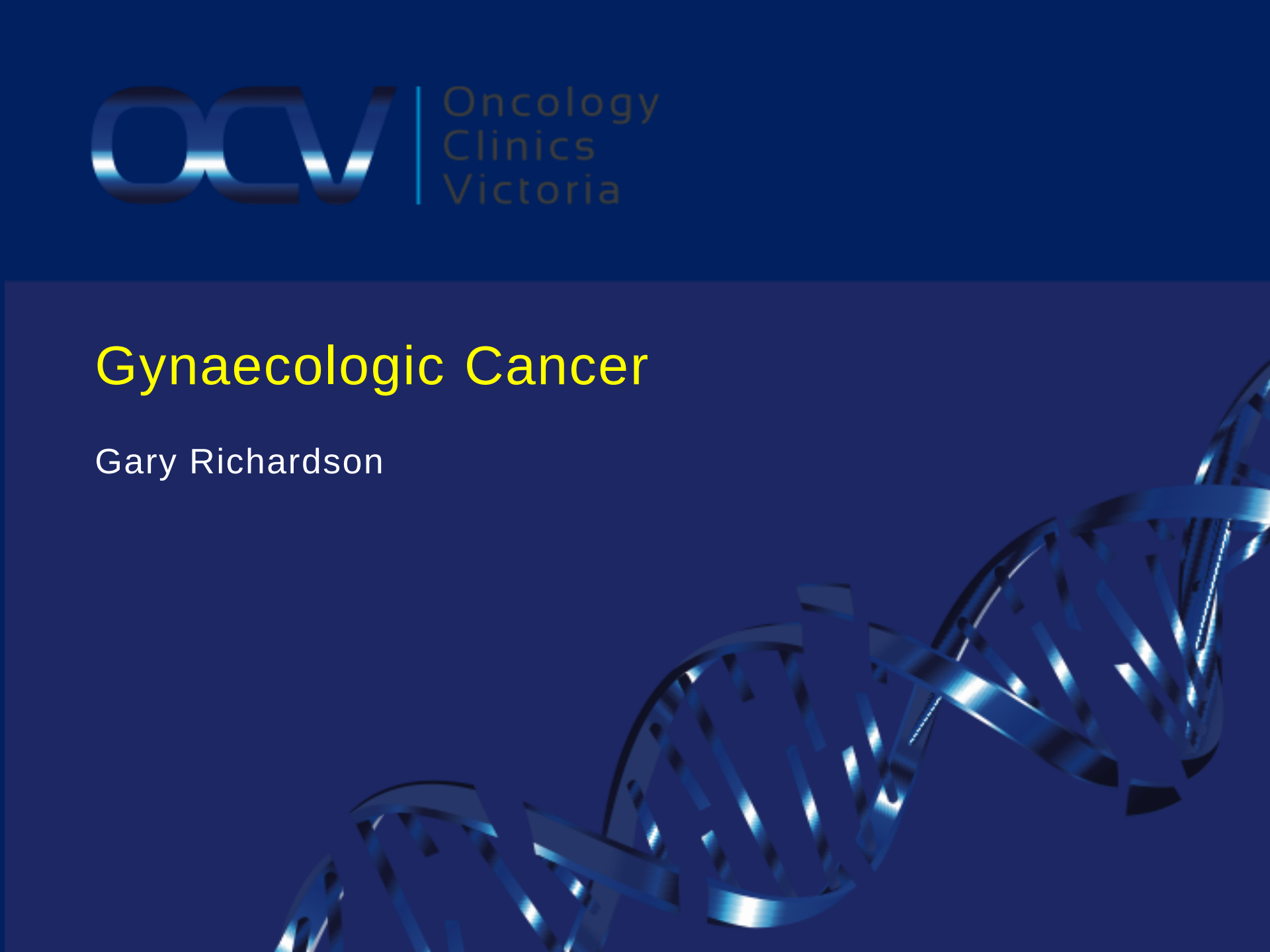
Oncology Clinics Victoria

Gynaecologic Cancer

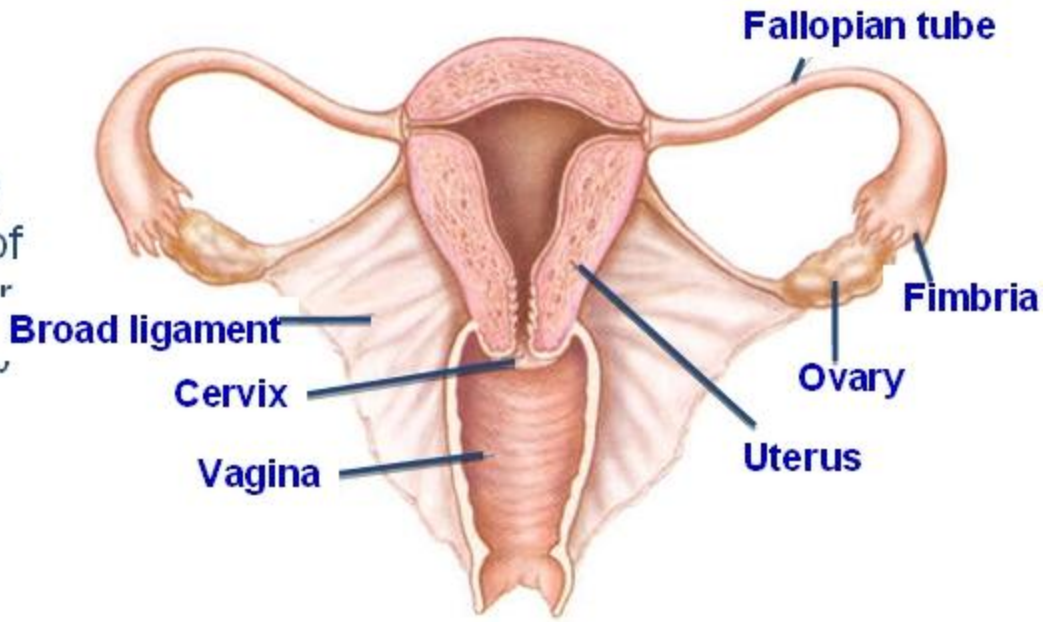
Gary Richardson



Gynecologic Cancers

Gynecologic (GYN) cancers include cancers of the female genital tract.

- Among the GYN cancers, uterine cancers are the most frequent in the United States, followed by cancers of the ovary and cervix. Ovarian cancer has the highest mortality, followed by cancers of the uterus and cervix.
- Fallopian tube, vaginal and vulvar cancers are rare.
- Cervix cancer remains a worldwide problem, but is rare in the United States since Pap smear screening has become widespread.



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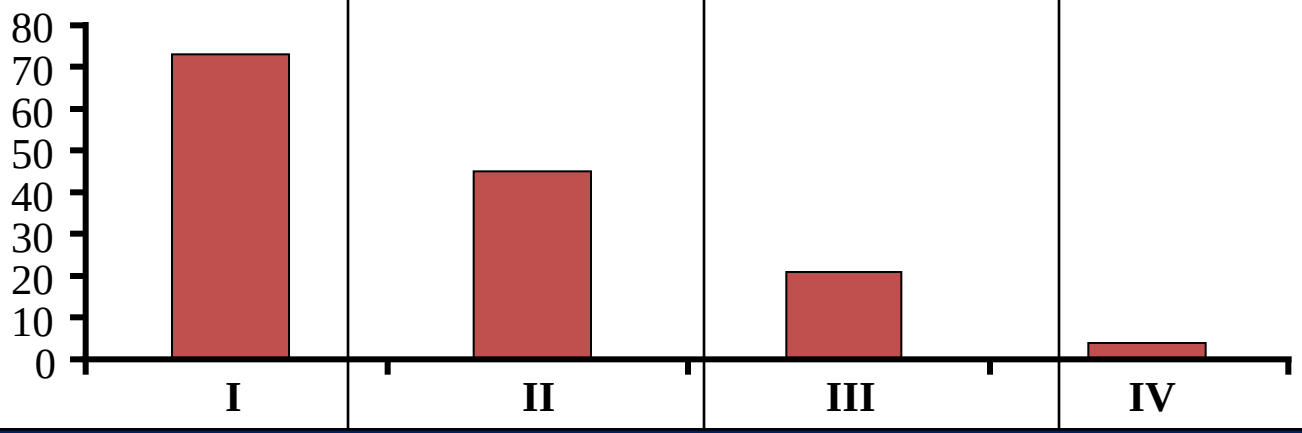
Ovarian Cancer

Ovarian Cancer: 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

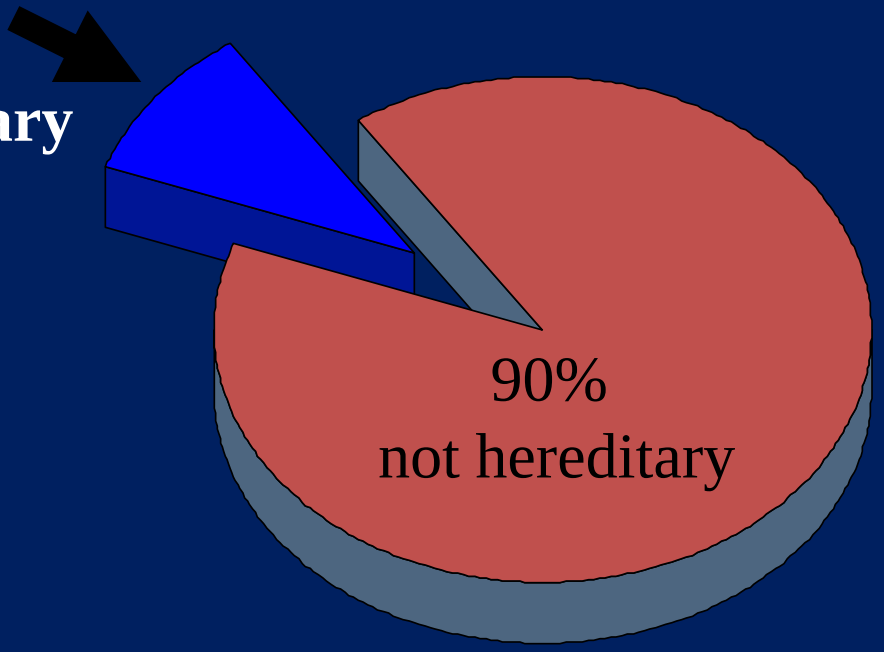
Stage	I	II	III	IV
Description	Confined to ovaries	Confined to pelvis	Confined to abdomen/lymph nodes	Distant metastases
Incidence	20%	5%	58%	17%
Survival	73%	45%	21%	< 5%



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

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.

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.

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

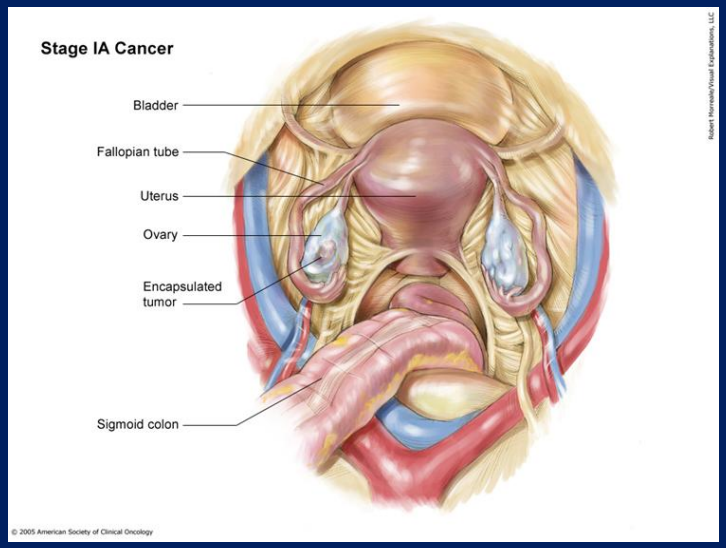
How is Ovarian Cancer Treated?

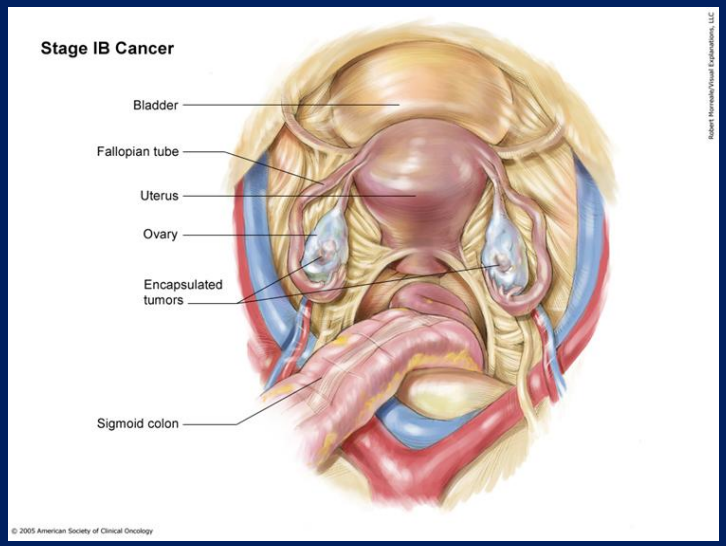
- Treatment depends on stage of cancer
- More than one treatment may be used
- Surgery
- Chemotherapy
- Radiation therapy

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

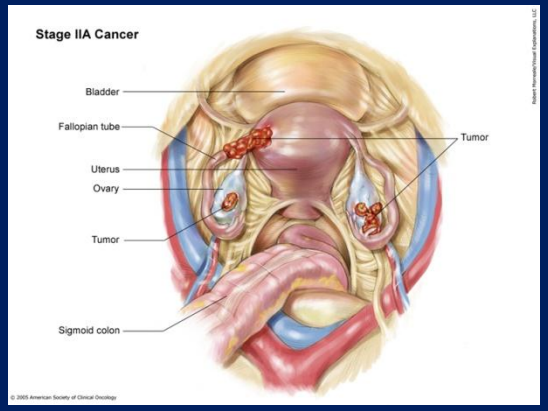
Stage I Ovarian Cancer

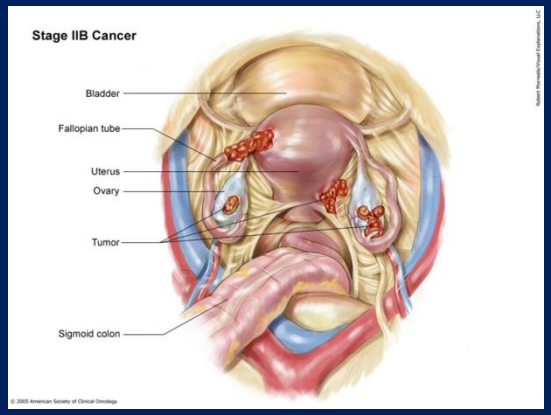


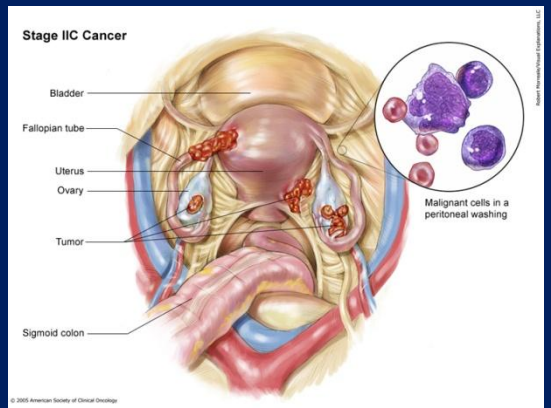


- Tumour is encapsulated and limited to ovaries
- No spread to lymph nodes or other parts of the body

Stage II Ovarian Cancer

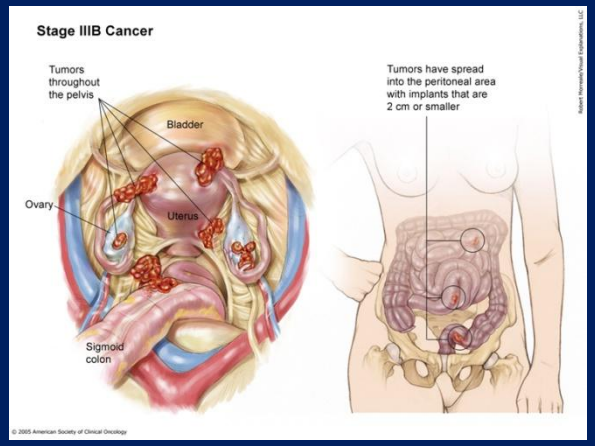


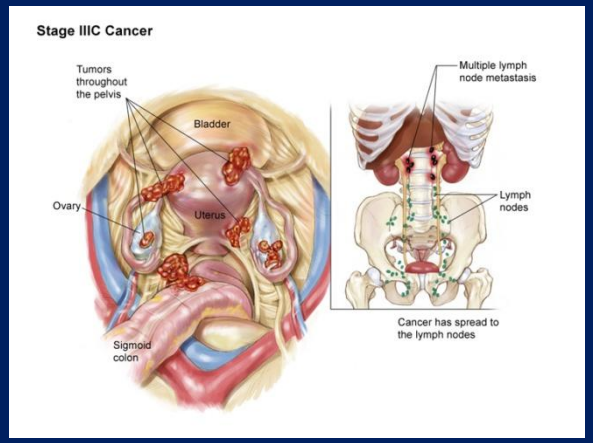




- Cancer is in one or both ovaries and has spread to the pelvis
- Cancer has spread to the uterus or fallopian tubes
- No spread to lymph nodes or other parts of the body

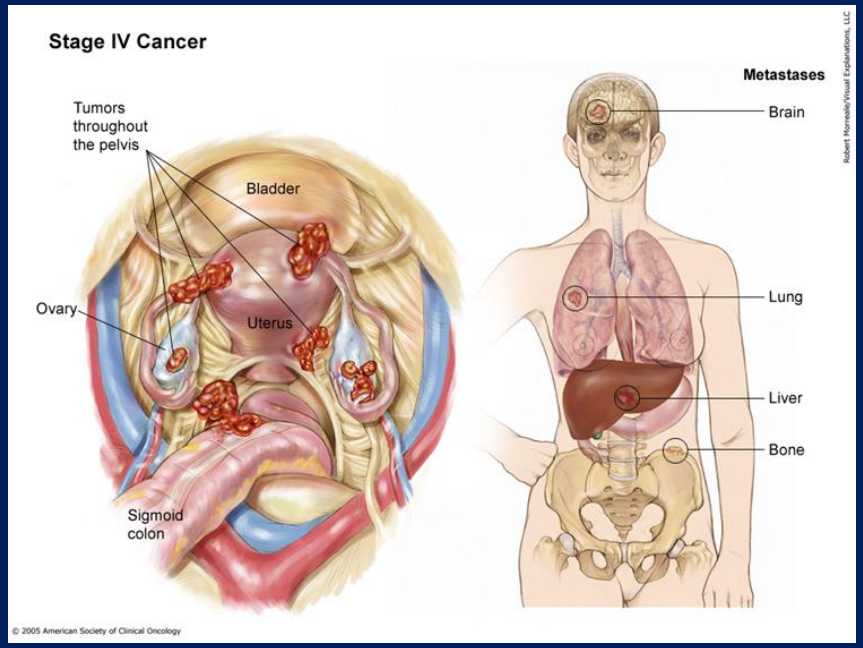
Stage III Ovarian Cancer





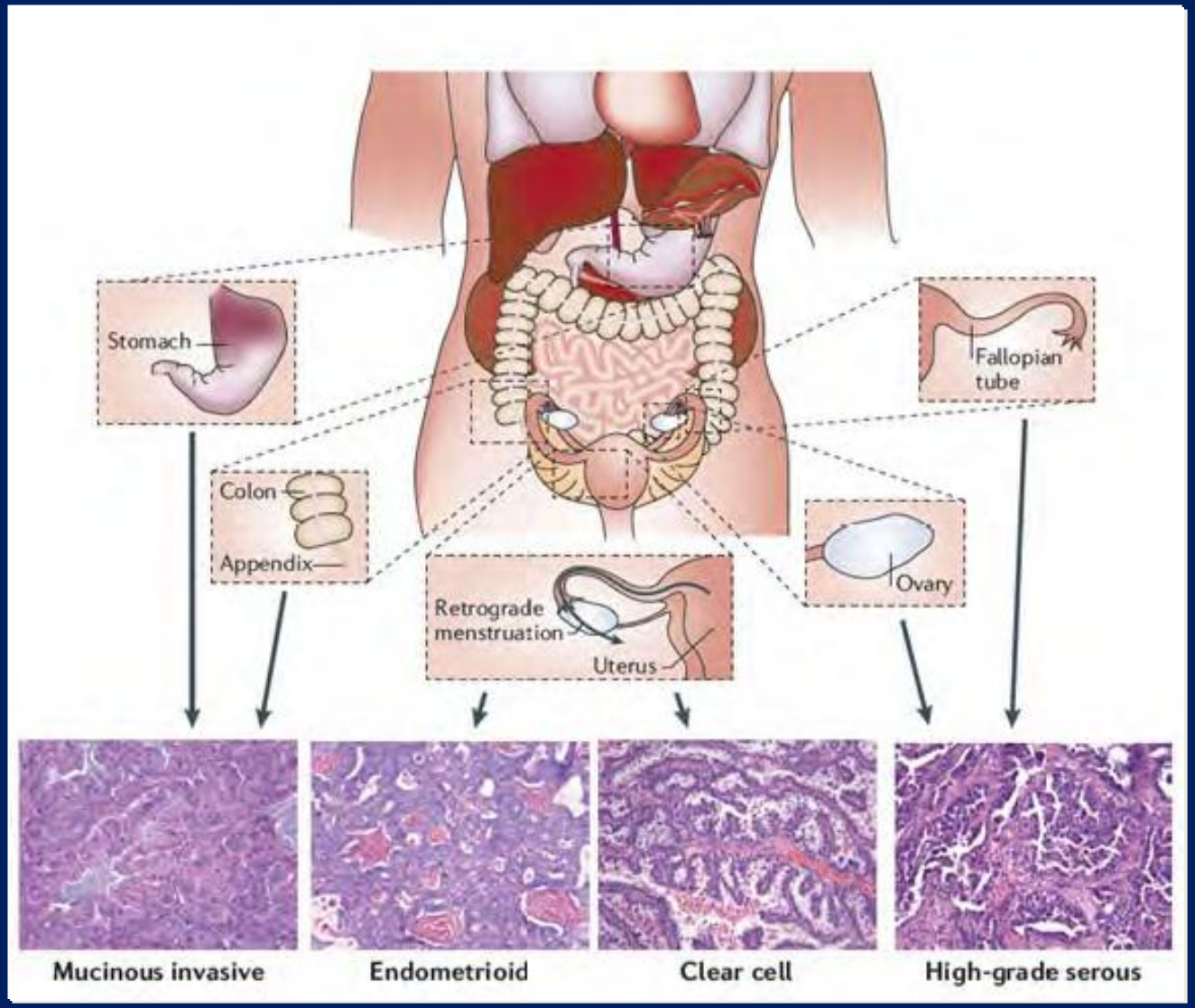
- Cancer is in one or both ovaries
- Cancer has spread beyond the pelvis into abdominal cavity
- Cytology -/+

Stage IV Ovarian Cancer



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

Cellular Classification



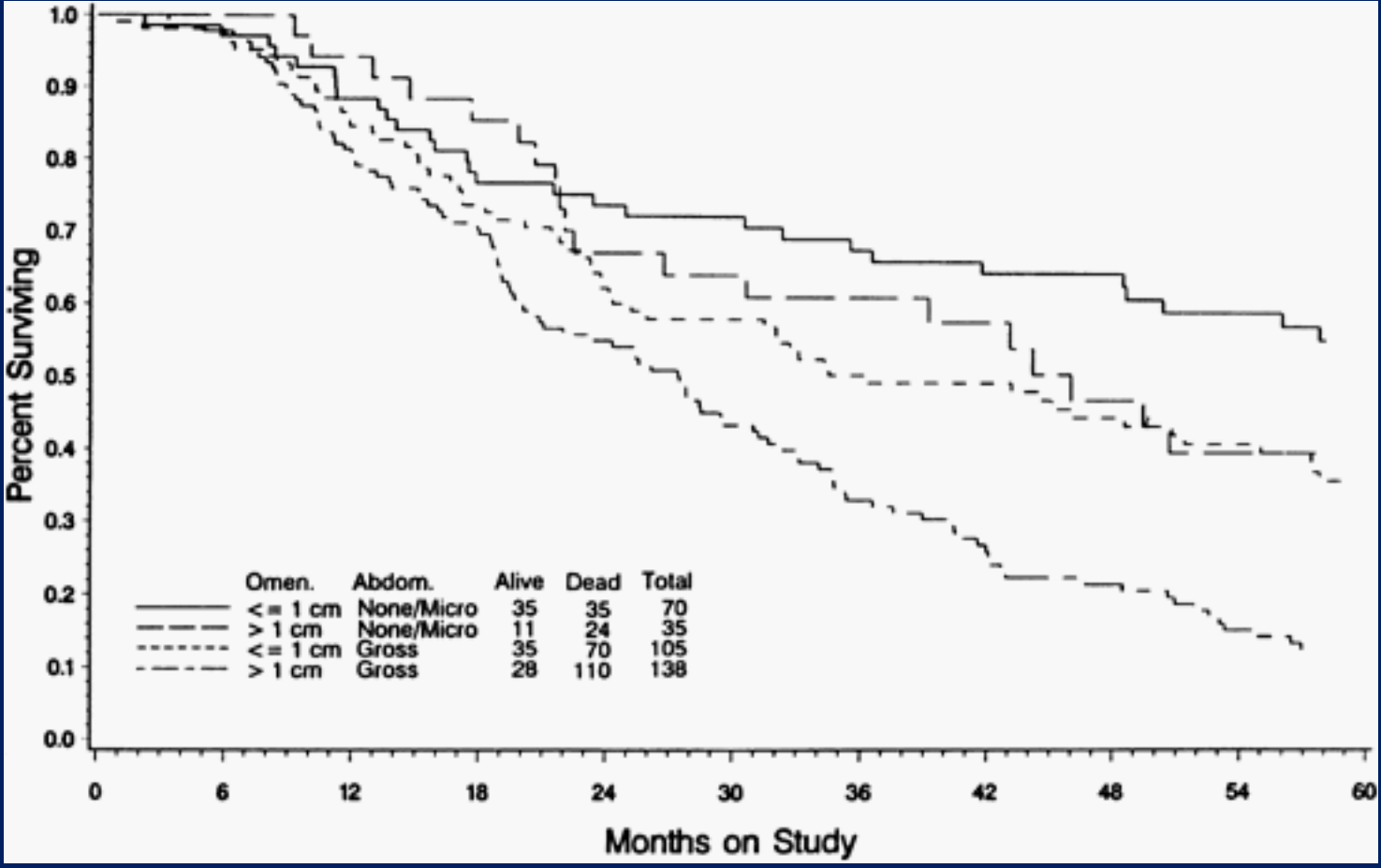
Prognostic Features

- 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 - III

- Radical Debulking Surgery
- Systemic Chemotherapy
- Combination chemotherapy regimens containing platinum have been shown to produce higher response rates and a prolongation of survival compared to drug regimens without platinum.

Treatment: Stage IV Disease

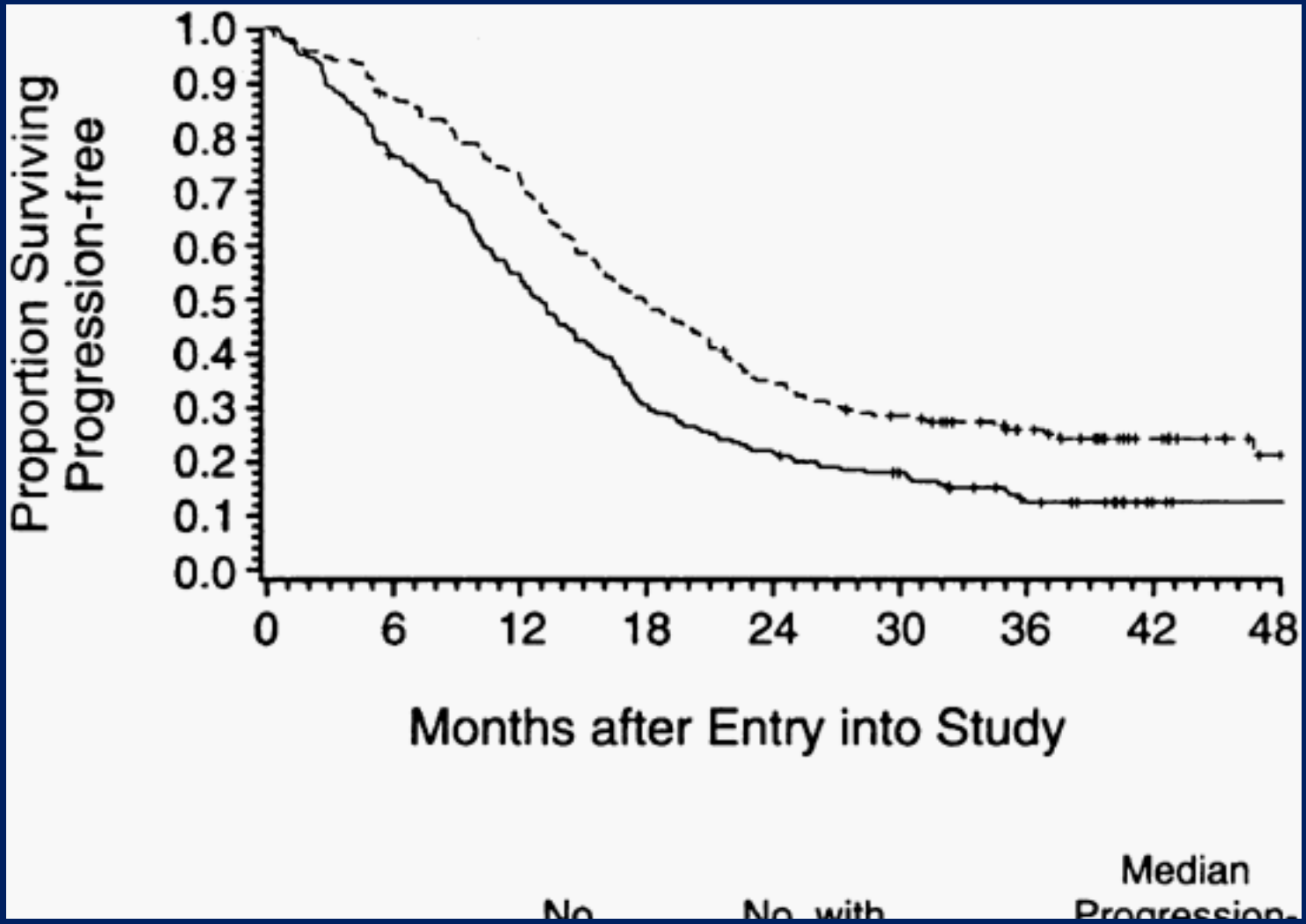
- Incurable cancer.
- Although many patients with stage IV disease undergo cytoreductive surgery, whether this improves survival has not been established.
- Intravenous chemotherapy.
- These patients should be considered for clinical trials involving novel therapies.

Ovarian Cancer: Initial Chemotherapy

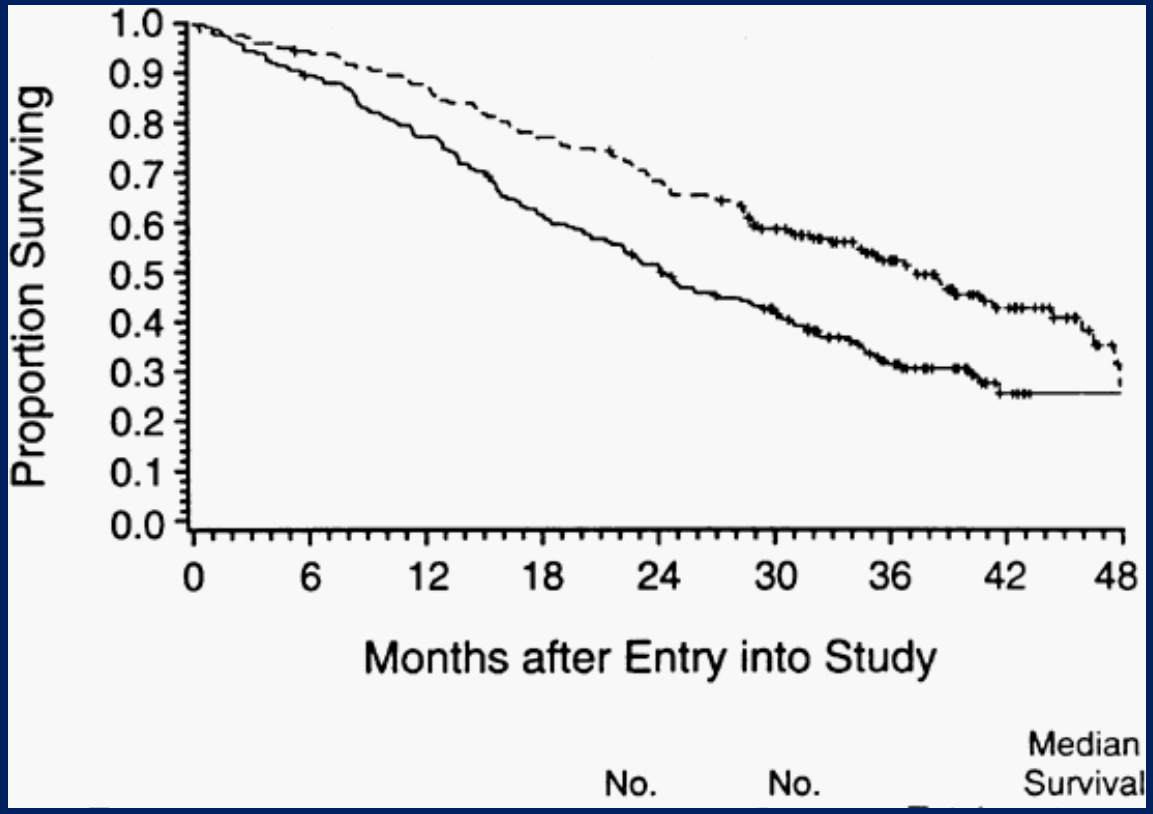
- Standard *frontline* chemotherapy is paclitaxel 175 mg/m^2 plus carboplatin AUC 6-7, every 21 days for 6 cycles
- Result of several studies over last decade
  - GOG 111[1] and OV 10[2]: paclitaxel/cisplatin vs cyclophosphamide/cisplatin
  - GOG 158[3] and AGO OVAR-3[4]: carboplatin instead of cisplatin

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



Change in Schedule

Schema of JGOG 3016

Katsumata, Lancet 2009; 374: 1331

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

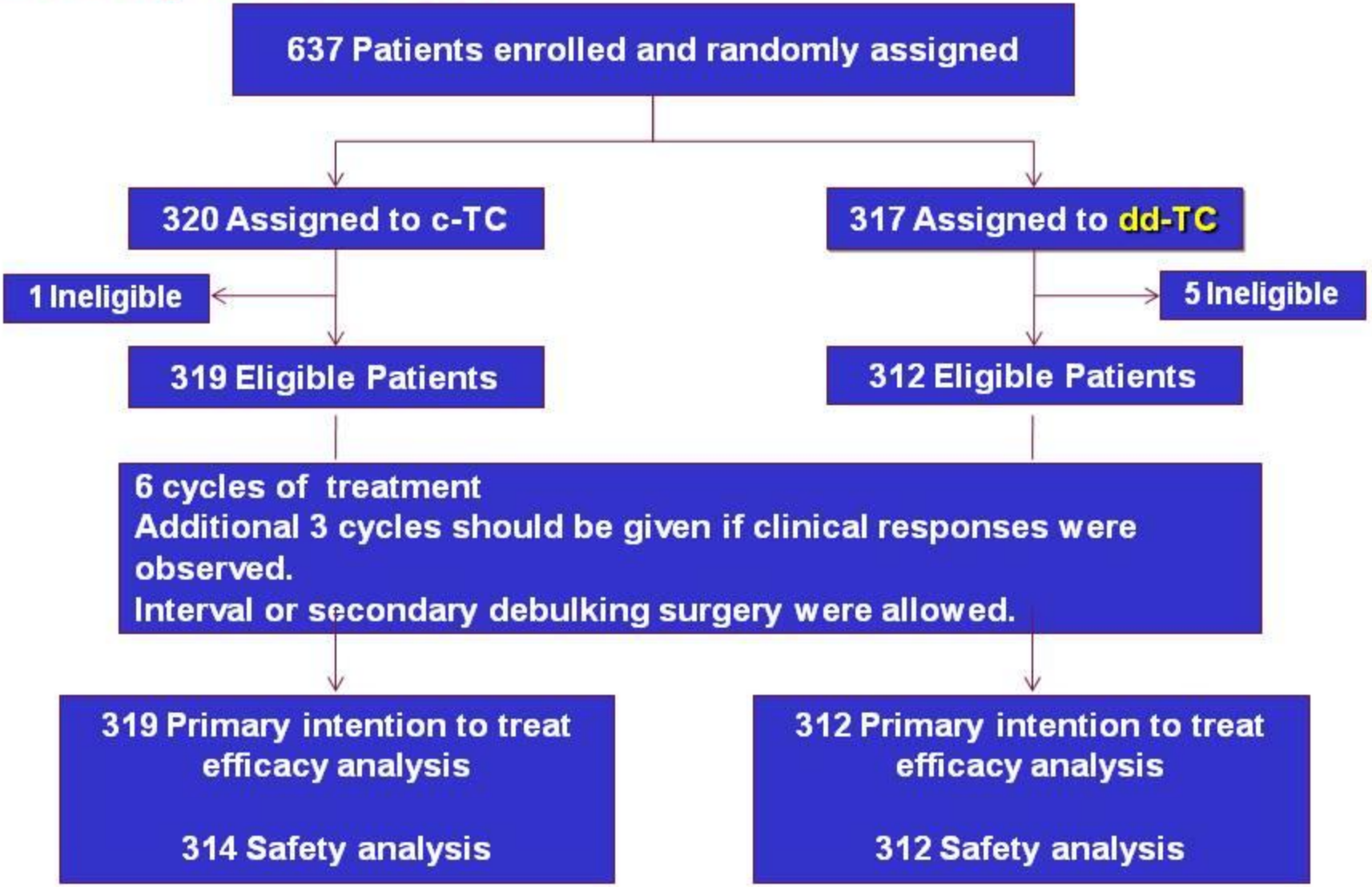
Randomization

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

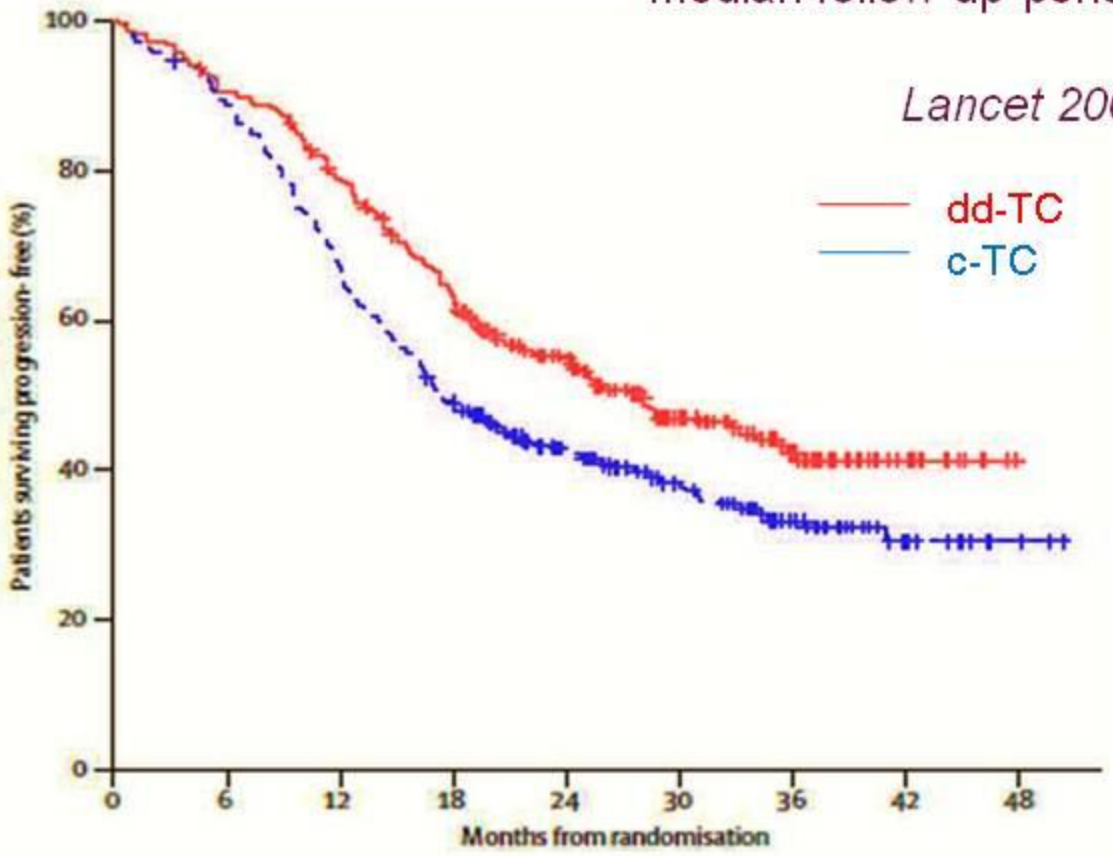
Evaluated by NCI-CTC ver.2.0

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

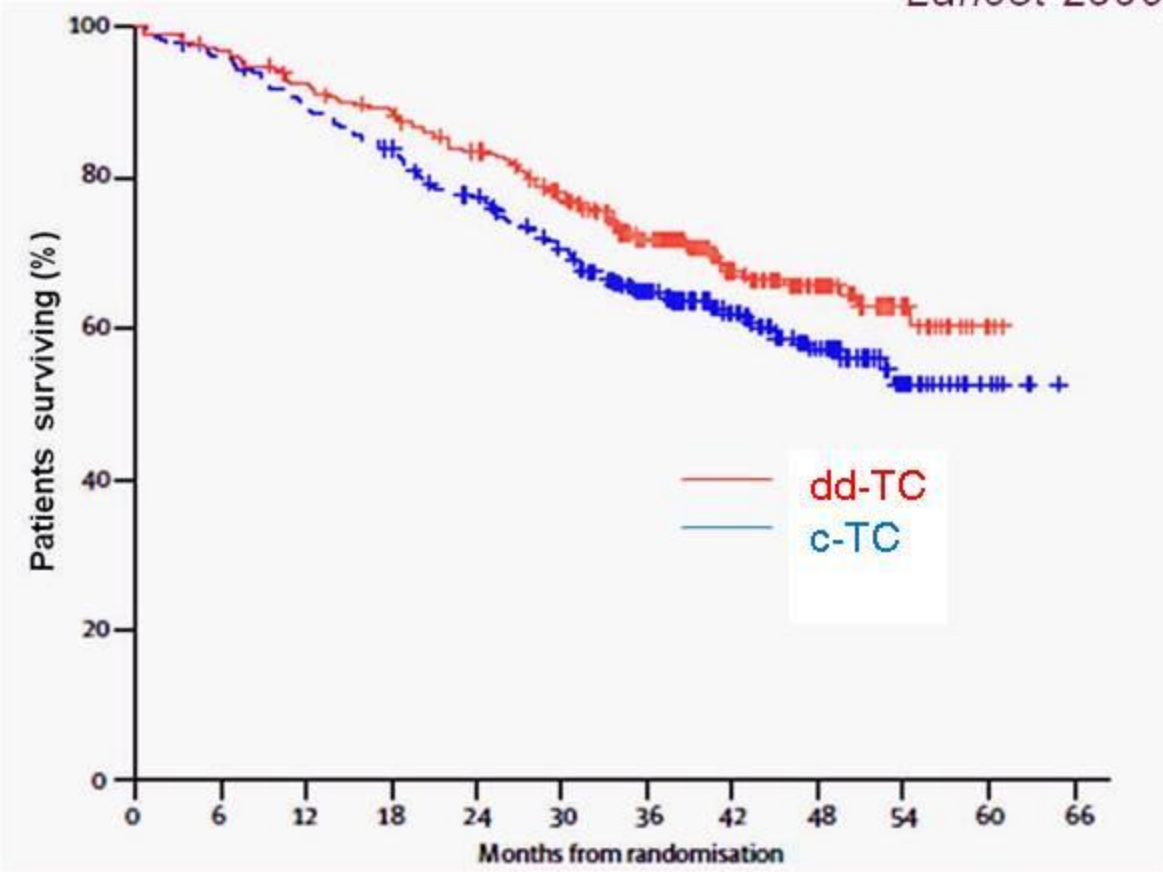
Lancet 2009; 374: 1331–38



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

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	

Copyright © 2006 Massachusetts Medical Society. All rights reserved. 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	

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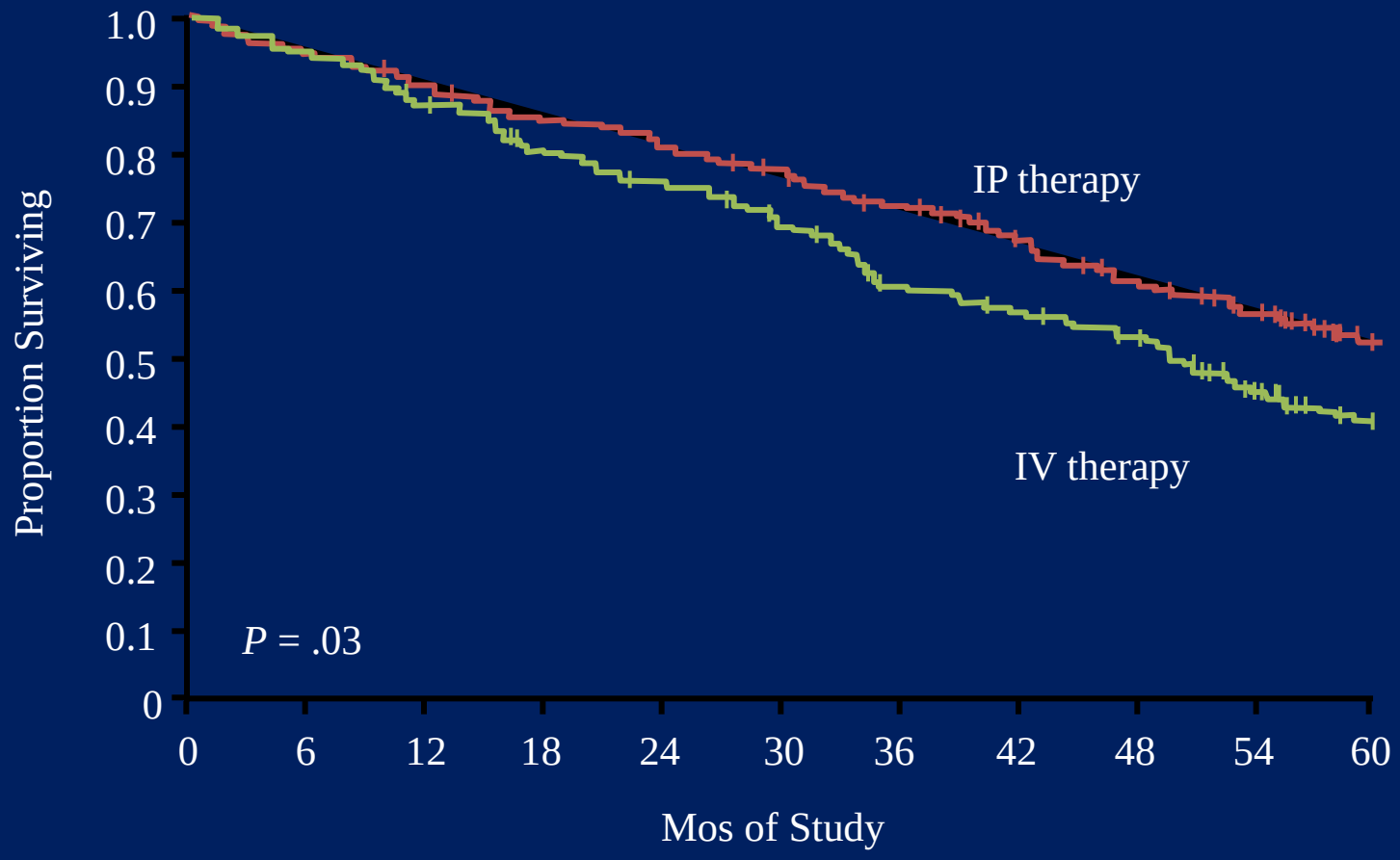
GOG 172: OS



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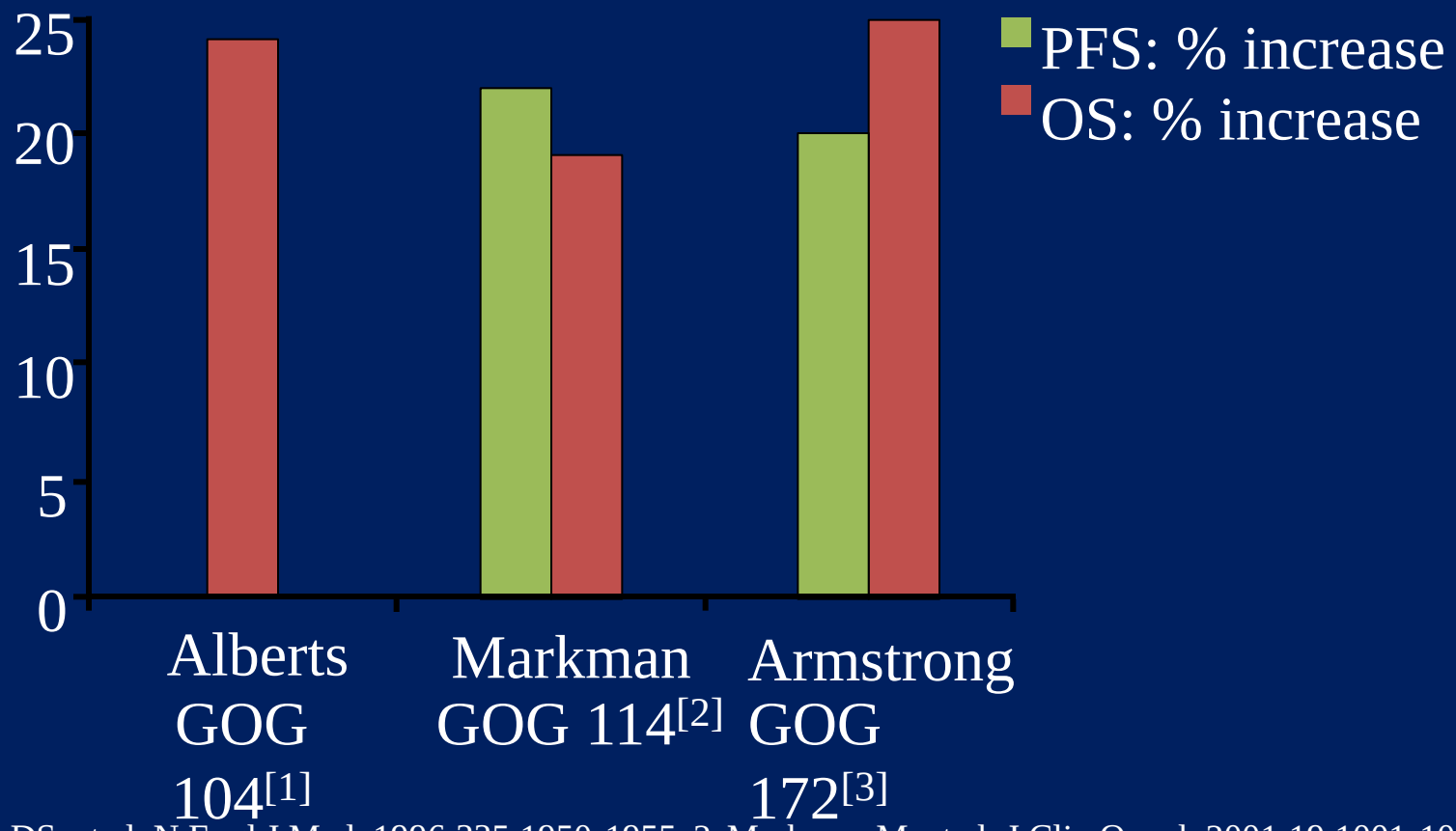
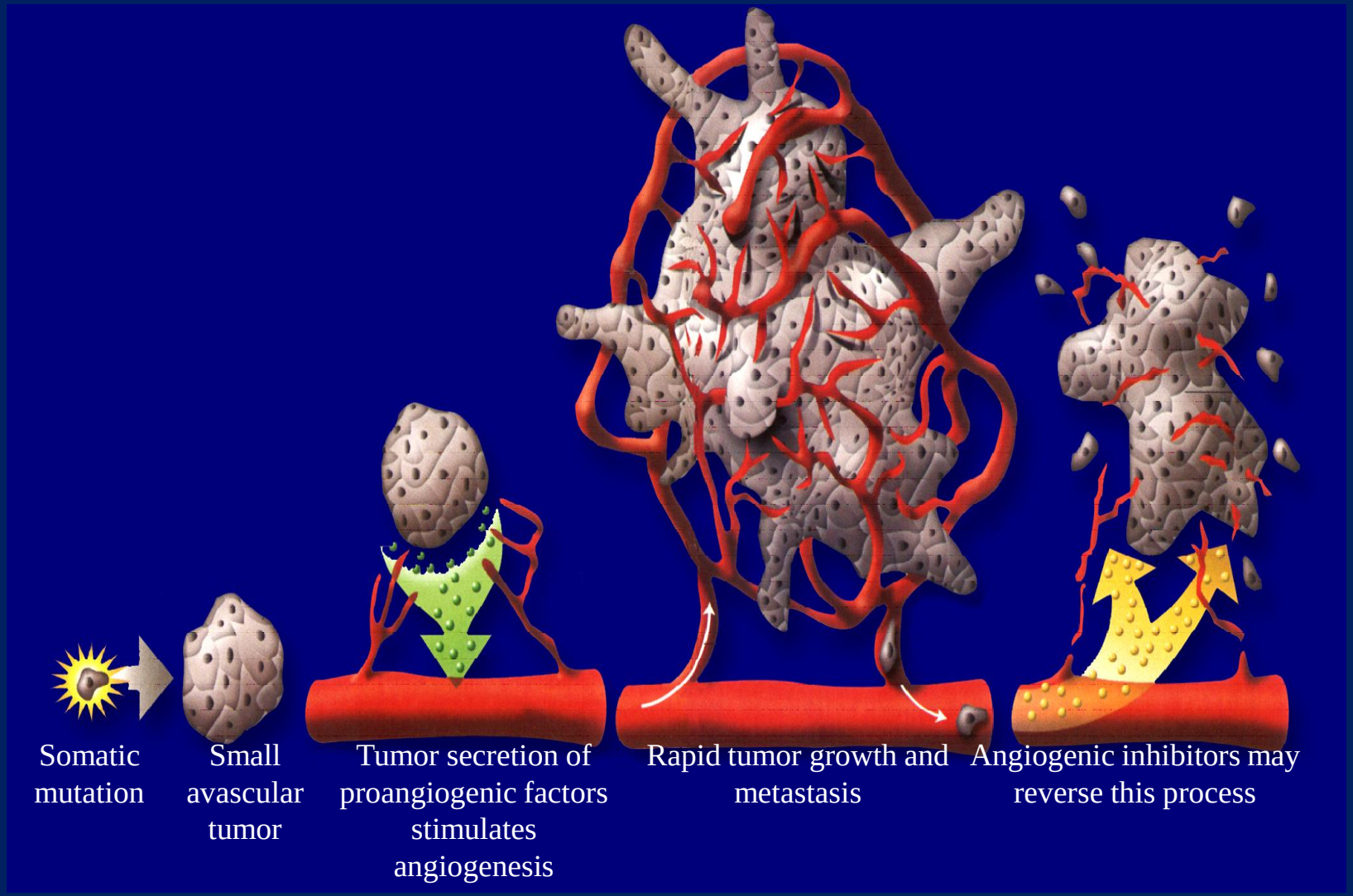
IP Compared With IV Chemotherapy Phase III Trials



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.

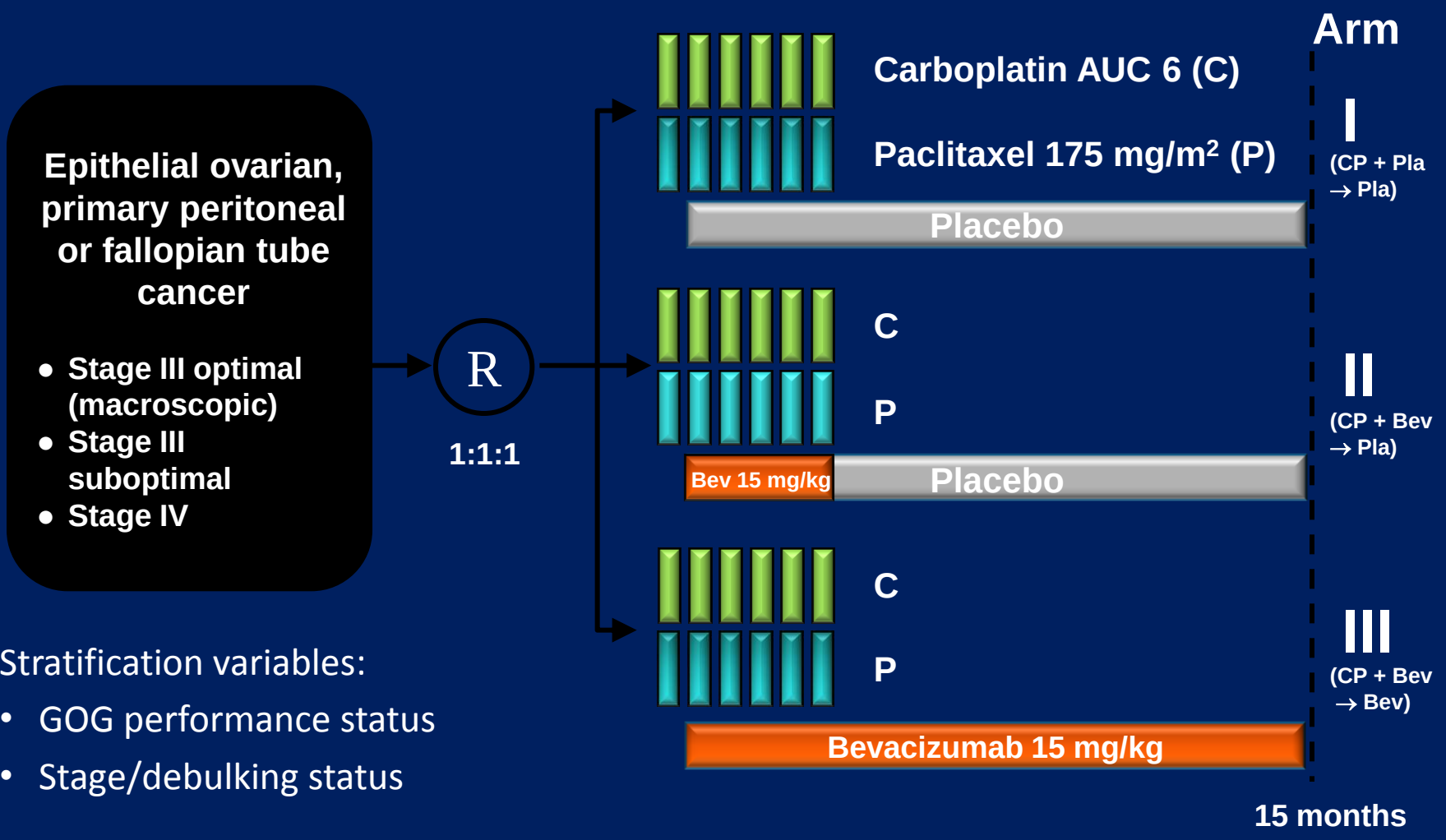
Will Adding a Targeted Therapy Help?

Angiogenesis as an Anticancer Treatment



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

GOG-0218: Study design



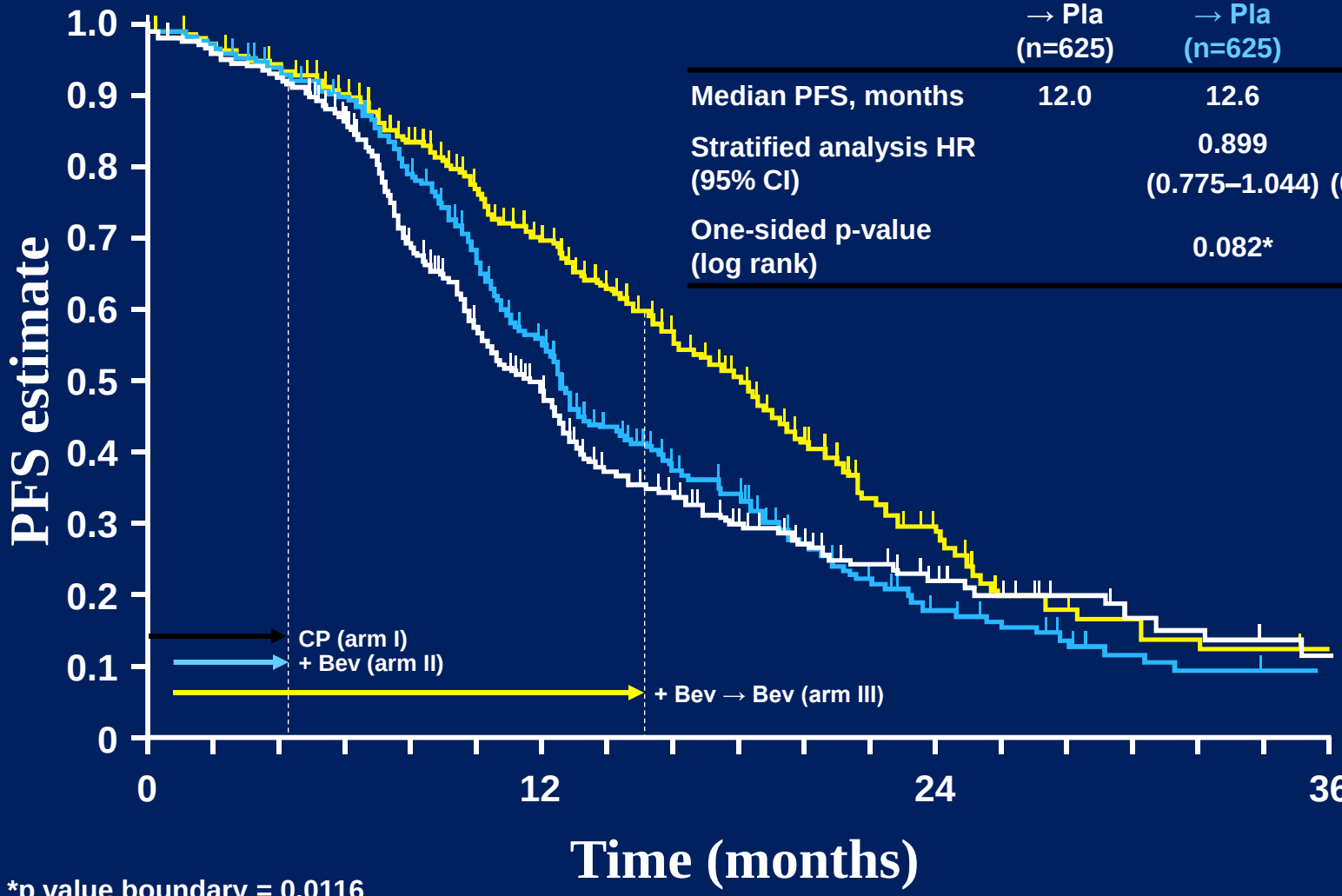
Stratification variables:

- GOG performance status
- Stage/debulking status

Burger et al. ASCO 2010

GOG-0218: Regulatory PFS analysis

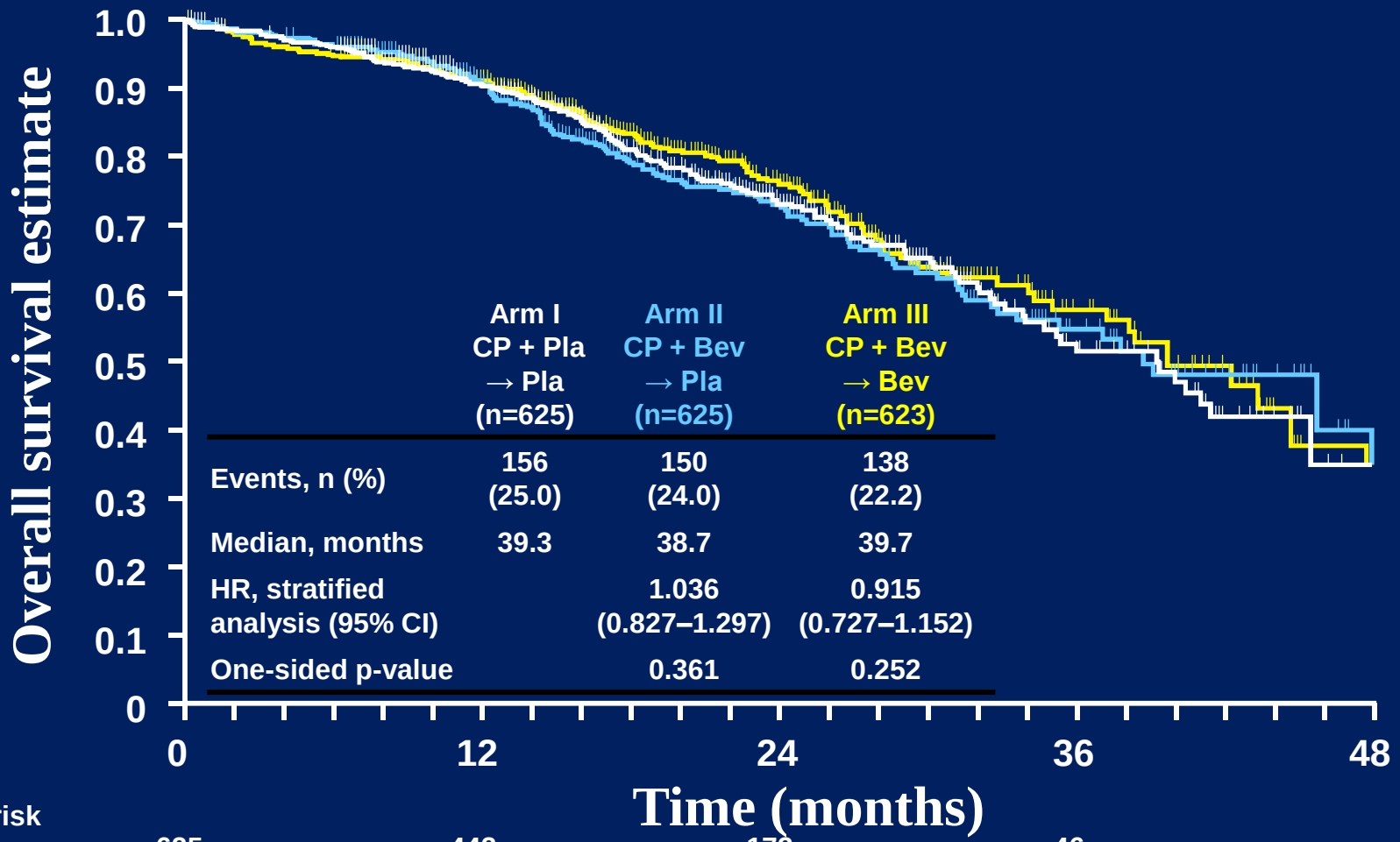
	Arm I CP + Pla → Pla (n=625)	Arm II CP + Bev → Pla (n=625)	Arm III CP + Bev → Bev (n=623)
Median PFS, months	12.0	12.6	18.0
Stratified analysis HR (95% CI)		0.899 (0.775–1.044)	0.645 (0.551–0.756)
One-sided p-value (log rank)		0.082*	<0.0001*



*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

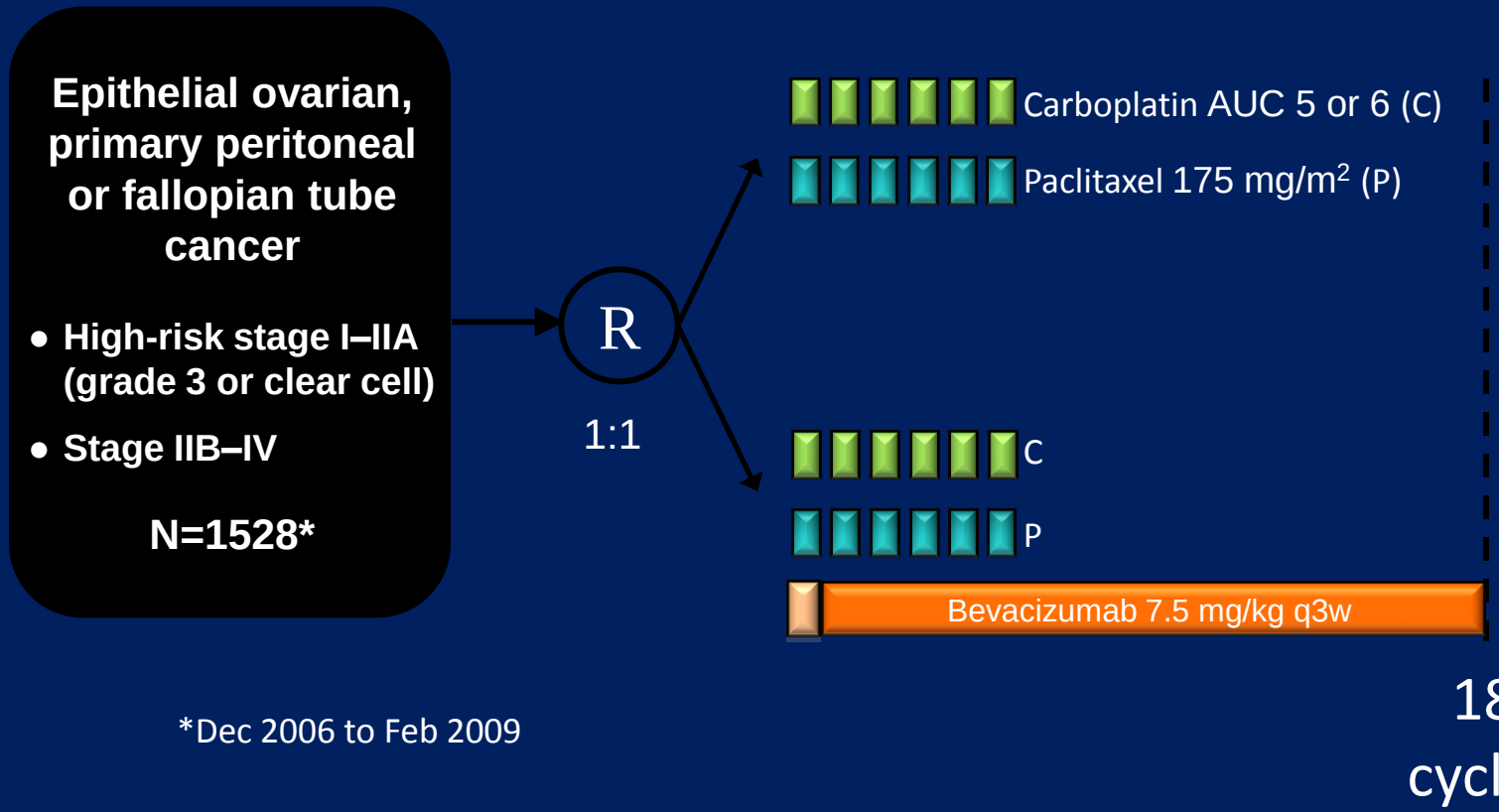
ICON7: A phase III Gynaecologic Cancer InterGroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer

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

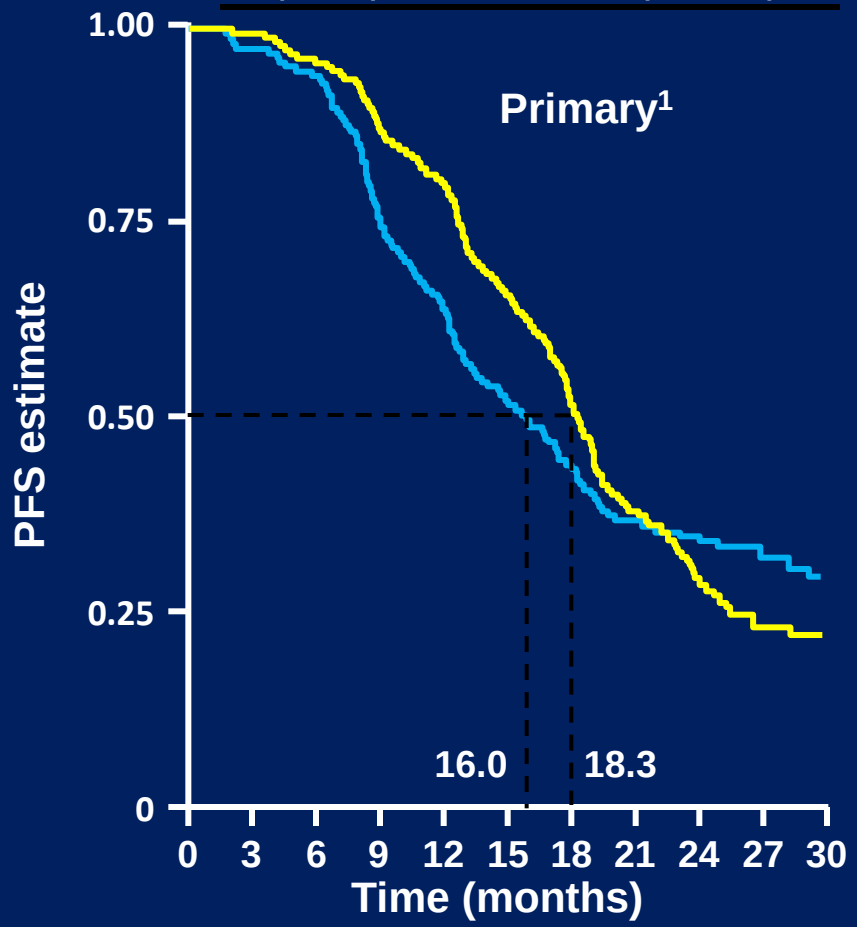
Stratification variables:

- 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

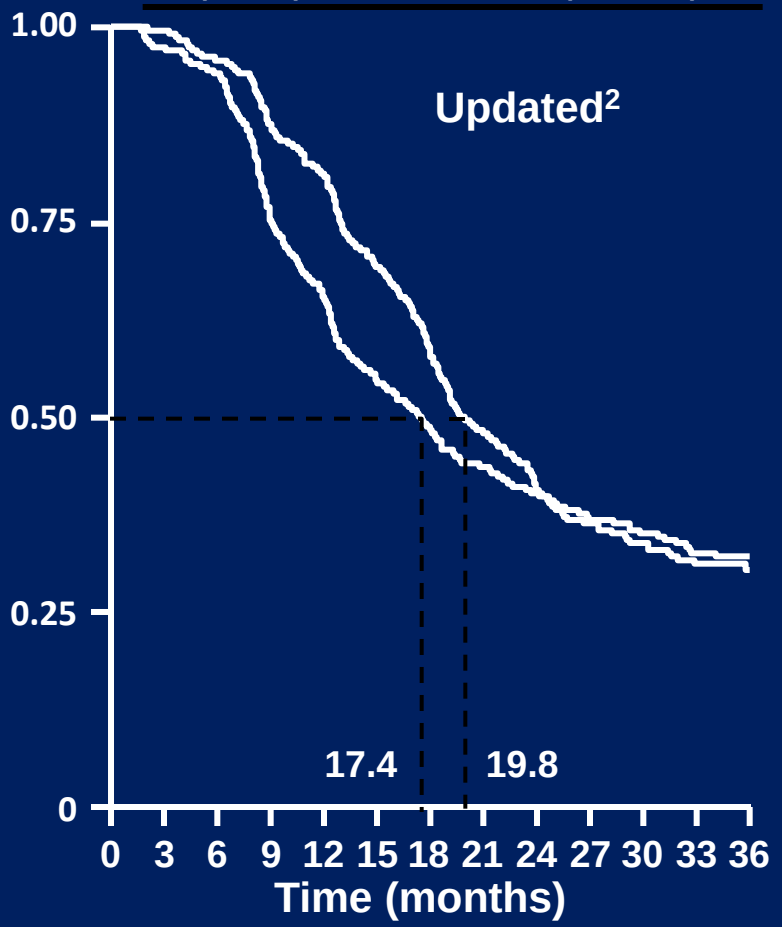
Perren et al. ESMO 2010

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)	

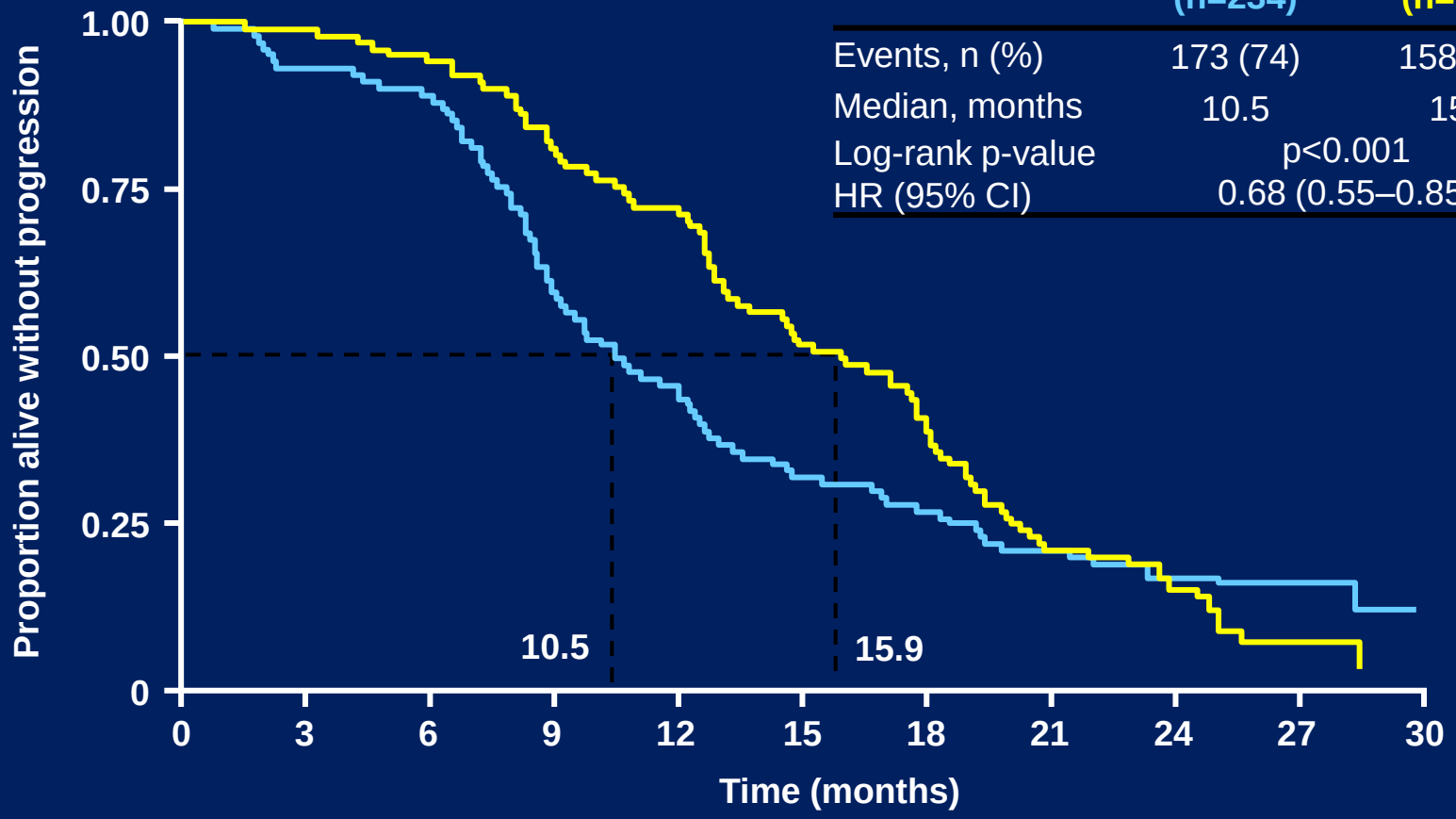


	CP (n=764)	CP + Bev (n=764)
Events, n (%)	464 (61)	470 (62)
Median, months	17.4	19.8
Log-rank p-value	0.039	
HR (95% CI)	0.87 (0.77–0.99)	



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

ICON7: PFS (high-risk subgroup)



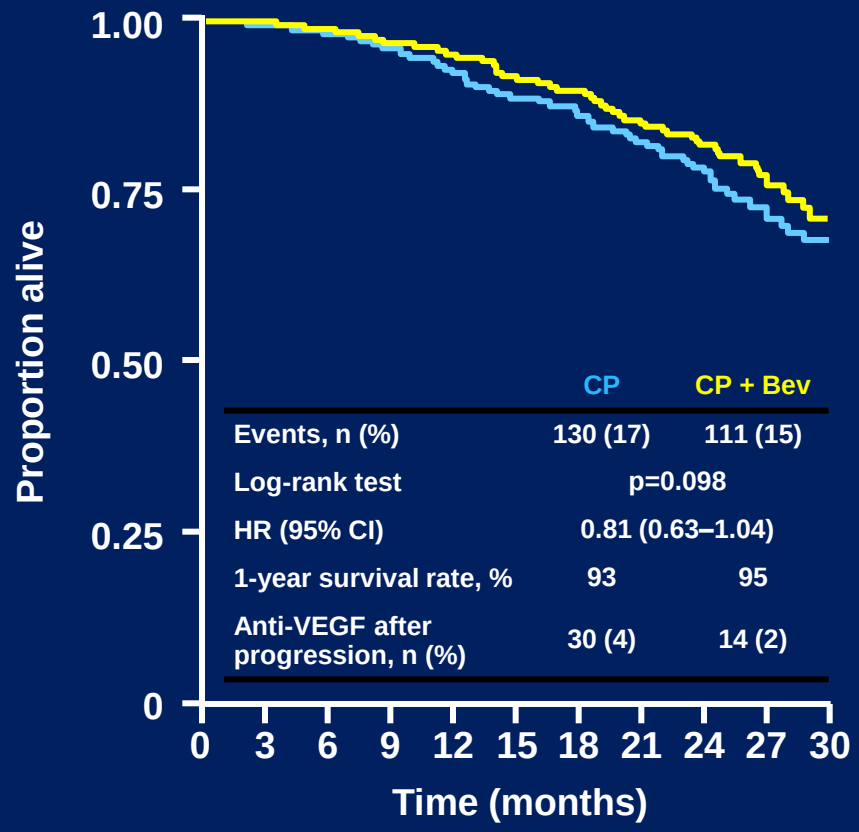
	CP (n=234)	CP + Bev (n=231)
Events, n (%)	173 (74)	158 (68)
Median, months	10.5	15.9
Log-rank p-value	p<0.001	
HR (95% CI)	0.68 (0.55–0.85)	

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

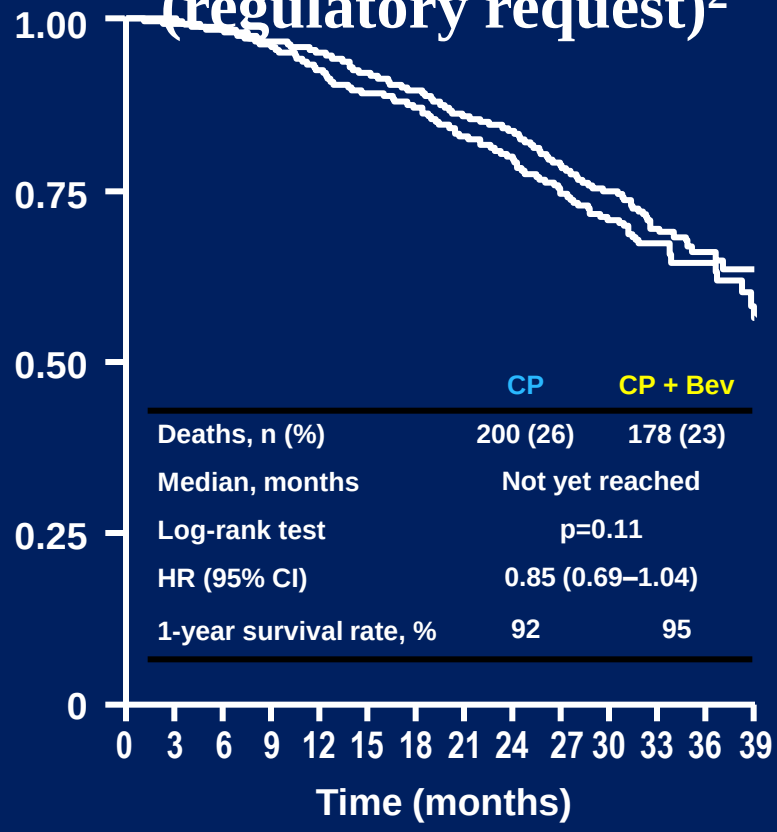
Preliminary analysis[1]



	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]

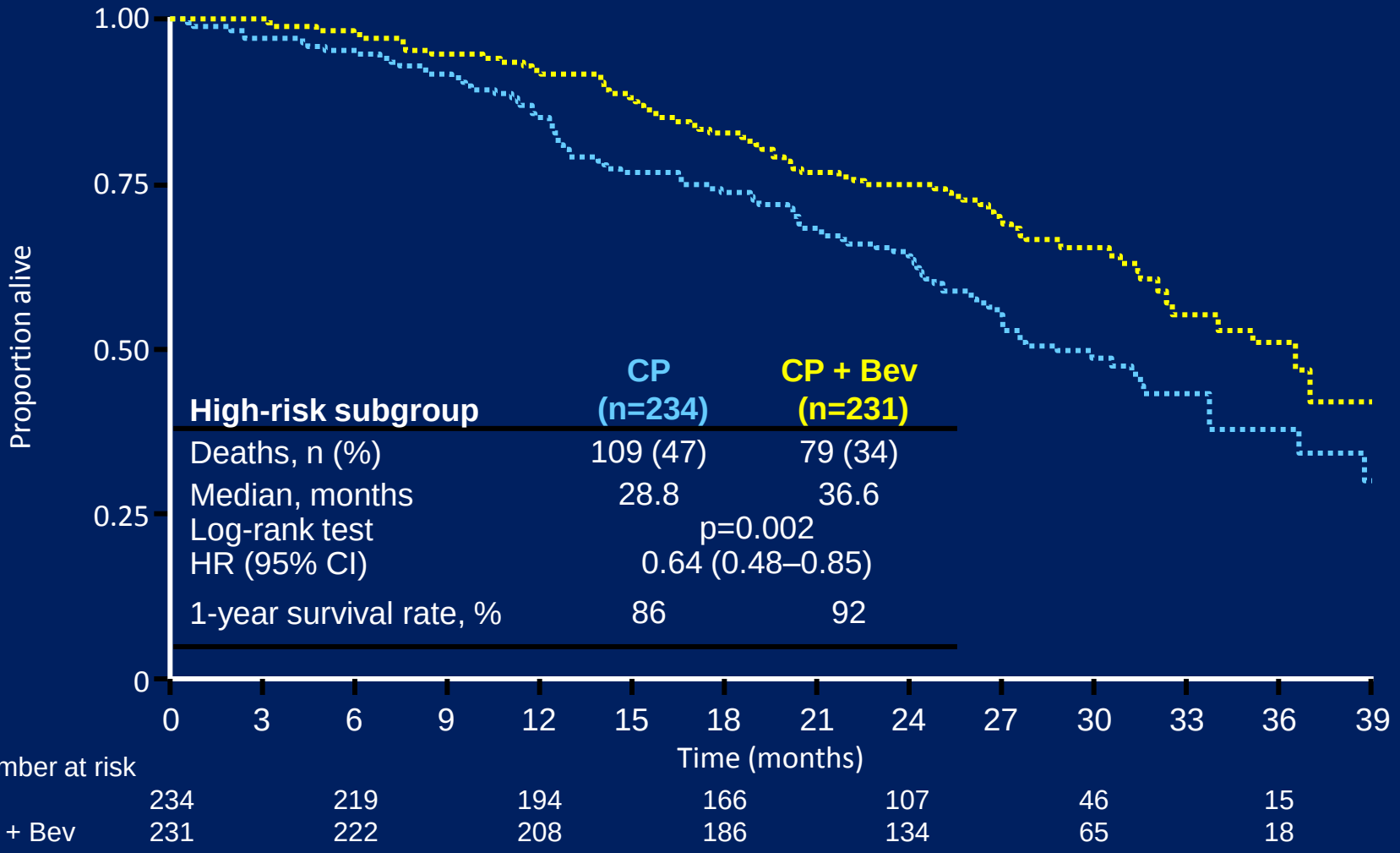


	CP	CP + Bev
Deaths, n (%)	200 (26)	178 (23)
Median, months	Not yet reached	
Log-rank test	p=0.11	
HR (95% CI)	0.85 (0.69–1.04)	
1-year survival rate, %	92	95

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

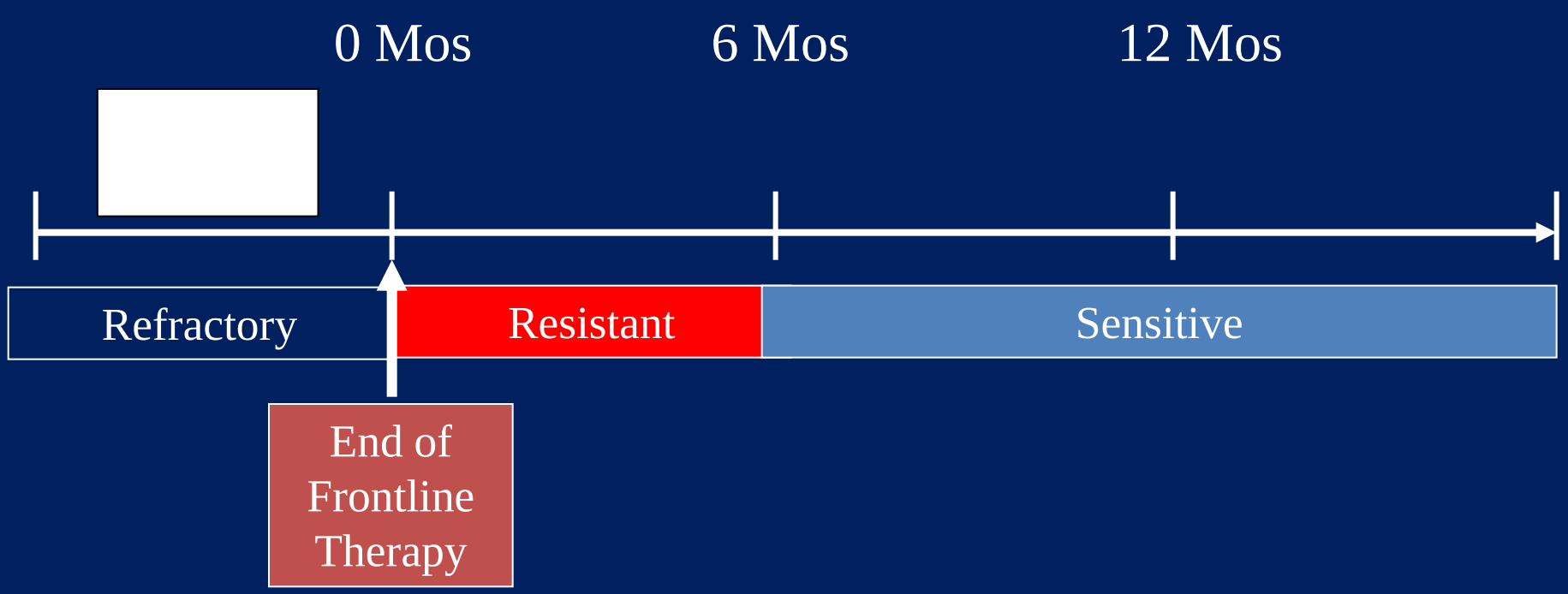
Background: Recurrent Ovarian Cancer

- 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

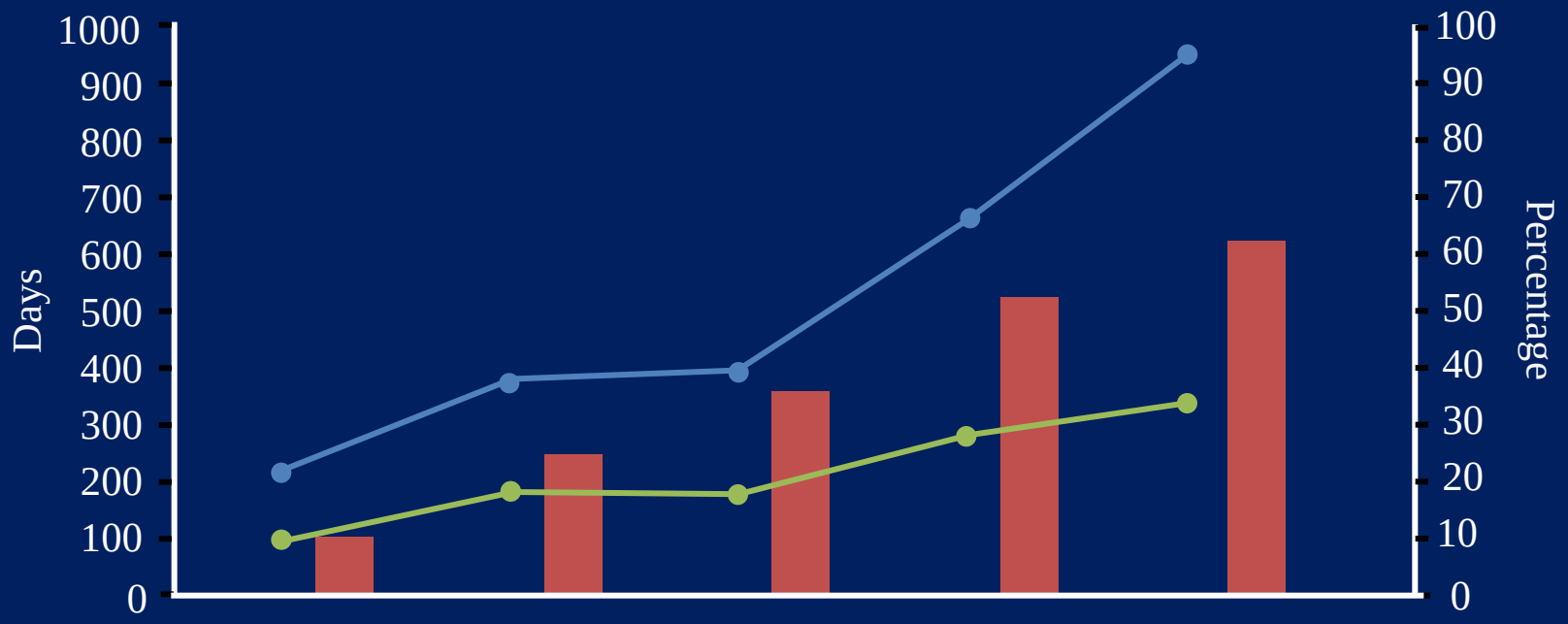
- How do you define recurrence?
  - Physical exam
  - Imaging
  - Chemical
- When do you treat?
  - Symptoms
  - Imaged lesions
  - Chemical

Platinum Sensitivity



Best Management Approaches for Patients With Platinum-Sensitive Recurrent Disease

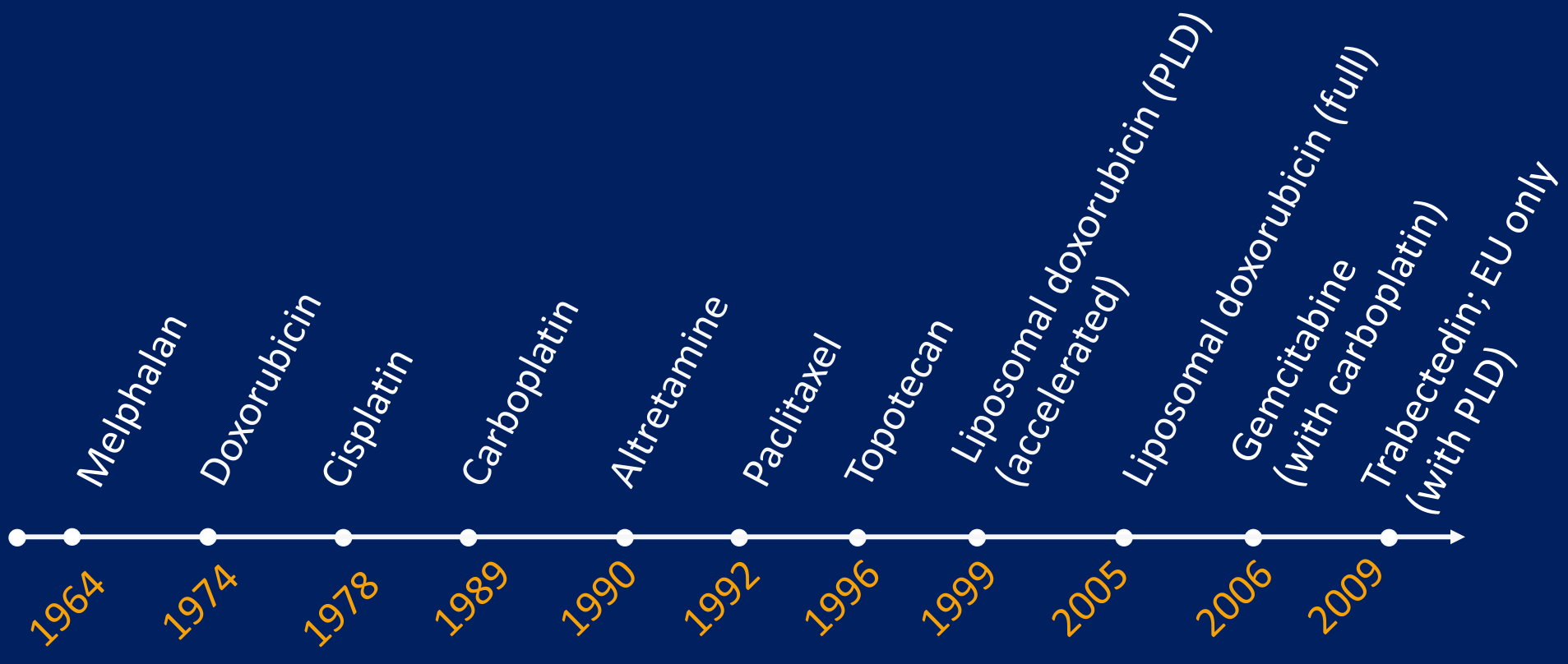
Recurrent Ovarian Cancer: Effect of Platinum-Free Interval and Survival



	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

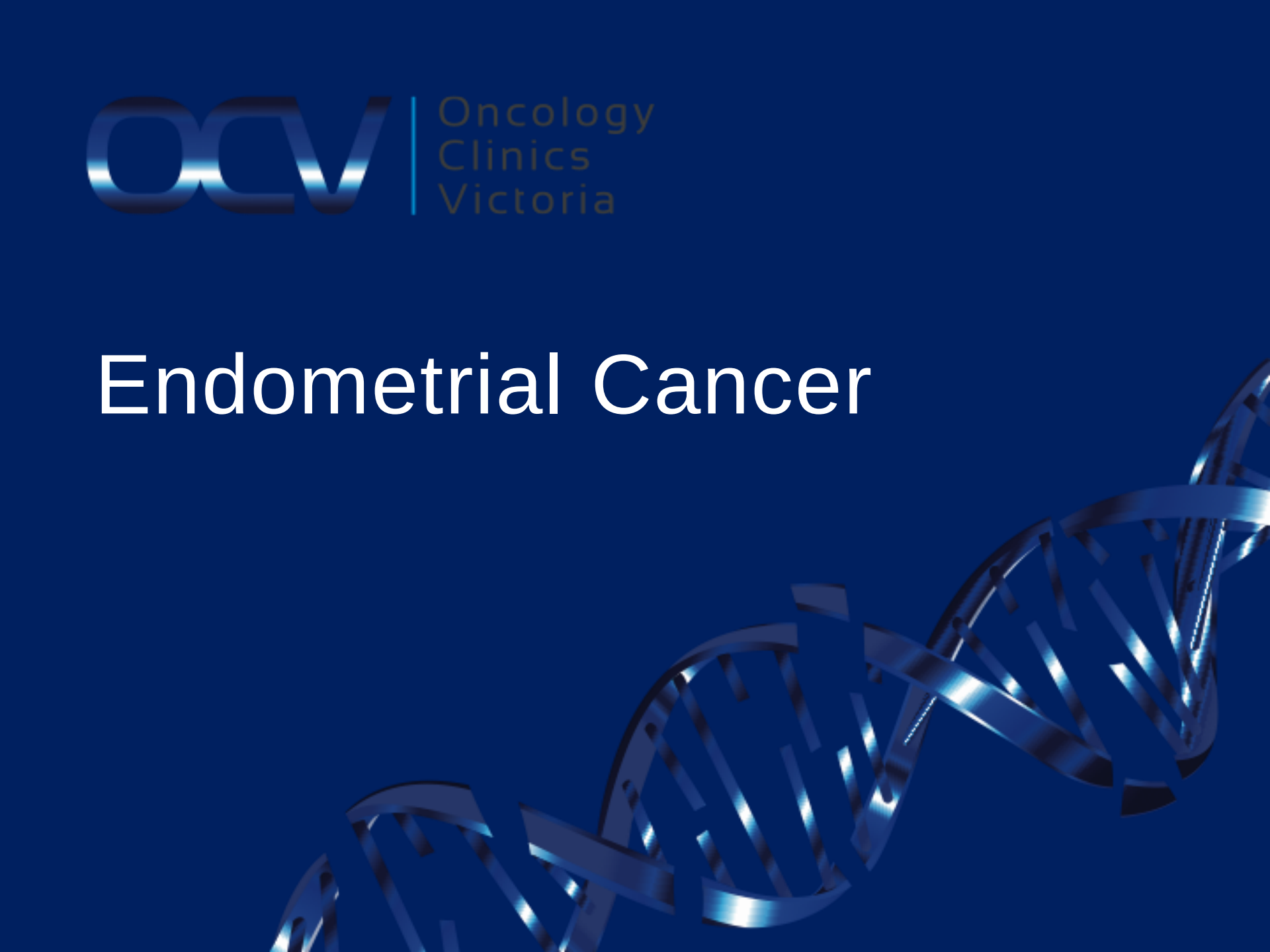
Pujade-Lauraine E, et al. ASCO 2002. Abstract 829.

FDA-Approved Drugs in Ovarian Cancer



Oncology Clinics Victoria

Endometrial Cancer



Endometrial Cancer

- Cancer of the endometrium is the most common gynaecological cancer.
- About 1900 Australian women, or about 15 women in every 100,000, are newly diagnosed with cancer of the uterus each year.
- Cancer of the uterus accounts for about 4 per cent of all cancers in Australian women.
- Endometrial cancer is most common in women who are over 50 years of age.

Endometrial Cancer - Symptoms

- **Vaginal bleeding and/or spotting in postmenopausal women**.
- Abnormal uterine bleeding, abnormal menstrual periods.
- Bleeding between normal periods in premenopausal women in women older than 40: extremely long, heavy, or frequent episodes of bleeding (may indicate premalignant changes).
- Anaemia, caused by chronic loss of blood. (This may occur if the woman has ignored symptoms of prolonged or frequent abnormal menstrual bleeding.)
- Lower abdominal pain or pelvic cramping.
- Thin white or clear vaginal discharge in postmenopausal women.

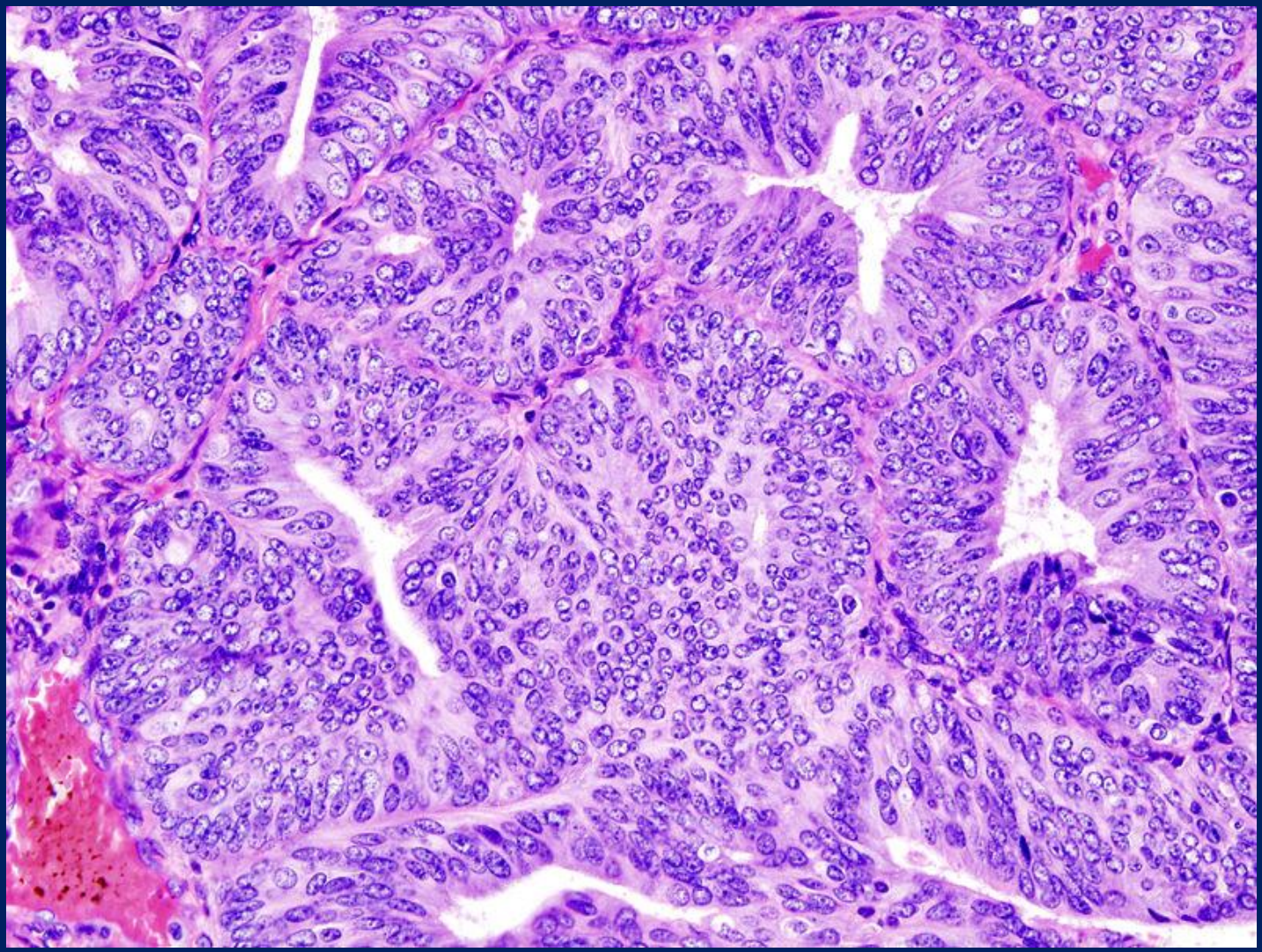
Risk Factors

- obesity - the larger the woman, the larger the risk
- high levels of oestrogen (unopposed oestrogen)
- endometrial hyperplasia
- hypertension
- polycystic ovary syndrome
- nulliparity
- early menarche & late menopause
- endometrial polyps or other benign growths of the uterine lining
- diabetes
- Tamoxifen
- high intake of animal fat
- pelvic radiation therapy
- breast cancer
- ovarian cancer

Diagnosis

- A Pap smear may be either normal or show abnormal cellular changes.
- Endometrial biopsy is the traditional diagnostic method. Both endometrial and endocervical material should be sampled.
- If endometrial biopsy does not yield sufficient diagnostic material, a dilation and curettage (D&C) is necessary for diagnosing the cancer.
- Hysteroscopy allows the direct visualization of the uterine cavity and can be used to detect the presence of lesions or tumours.
- Endometrial biopsy or aspiration may assist the diagnosis.
- Transvaginal ultrasound to evaluate the endometrial thickness in women with postmenopausal bleeding is increasingly being used to evaluate for endometrial cancer.

Endometrial Adenocarcinoma



FIGO Staging

Stage I	Tumour confined to uterus	
	IA	Tumour confined to the uterus, no or < ½ myometrial invasion
	IB	Tumour confined to the uterus, > ½ myometrial invasion
Stage II	Cervical stromal invasion	
Stage III	Tumour invades pelvis	
	IIIA	Tumour invades serosa or adnexa
	IIIB	Vaginal and/or parametrial involvement
	IIIC1	Pelvic lymph node involvement
	IIIC2	Para-aortic lymph node involvement, with or without pelvic node involvement
Stage IV	Distant disease	
	IVA	Tumour invasion bladder mucosa and/or bowel mucosa
	IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

Survival Rates

Stage	5 year survival rate
I-A	90%
I-B	88%
I-C	75%
II	69%
III-A	58%
III-B	50%
III-C	47%
IV-A	17%
IV-B	15%

Pre-Operative Work Up

- Clinical and gynaecological examination
- Trans-vaginal ultrasound
- Chest & Abdominal/pelvic CT scan
- Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best tool to assess the cervical involvement.
- [18F]Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT could be useful to detect distant metastases accurately.

Treatment

- Radical hysterectomy
- Post-operative radiation
  - Brachytherapy
  - External bean radiotherapy
- Hormonal Therapy
- Chemotherapy

Surgery

- Stage I: Hysterectomy alone. Routine systematic pelvic lymphadenectomy is not recommended.
- Stage II: Radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy.
- Stage III: Maximal surgical debulking is imperative in patients with a good performance status.
- Stage IV: Palliative surgery could be considered in patients with a good performance status after multidisciplinary decision making.

Radiotherapy

- At present there is great uncertainty regarding what is the optimal adjuvant treatment for localized endometrial cancer.
- In 2009, a randomized trial compared vaginal brachytherapy vs observation in stage IA G1–2 with a similar overall recurrence rate, survival and late toxicity in the two groups.
- External beam radiation has been shown to reduce the rate of locoregional recurrence in intermediate-risk endometrial cancer. However, three large randomized studies (PORTEC-1, GOG 99 and ASTEC MRC-NCIC CTG EN.5) failed to demonstrate that radiation improves overall or disease-specific survival.
- A randomized clinical trial (PORTEC-2) comparing vaginal brachytherapy and external beam radiation in intermediate-risk patients has failed to show any difference in overall survival or progression-free survival (PFS). The quality of life was better in the vaginal brachytherapy arm.

Chemotherapy

- Platinum-based chemotherapy can be considered in stage I G3 with adverse risk factors (patient age, lymphovascular space invasion and high tumor volume) and in patients with stage II–III [II, B].
- Maggi et al. conducted a randomized trial in 345 high-risk patients comparing five courses of cisplatin, doxorubicin and cyclophosphamide with external pelvic radiation. The authors reported no difference between therapies in terms of PFS or overall survival.
- A Japanese multicenter randomized trial compared whole-pelvic irradiation with three or more courses of cyclophosphamide, doxorubicin and cisplatin chemotherapy in patients with old stages IC–IIIC endometrioid adenocarcinoma. No difference in overall survival, relapse rate or PFS was observed.

Combined Chemo-radiation

- Two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE- III) were undertaken to clarify whether the sequential use of chemotherapy and radiotherapy improved PFS over radiation therapy alone in high-risk endometrial cancer patients (stage I–IIA, IIIC, any histology).
- The combined modality treatment was associated with 36% reduction in the risk of relapse or death [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.41–0.99; P = 0.04].
- Cancer-specific survival was significantly different (HR 0.55, CI 0.35–0.88; P = 0.01] and favoured the use of adjuvant chemotherapy in addition to radiotherapy.
- The ongoing PORTEC 3 study is comparing radiotherapy with the concomitant and sequential use of chemotherapy and radiotherapy in patients with endometrioid stage I grade 3, stage II–III and any stage serous and clear cell carcinomas.
- Current evidence does not support the use of progestins in adjuvant treatment of endometrial cancer [I, A].

Advanced Disease

- Systemic treatment for metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy.
- Hormonal therapy is recommended for endometrioid histologies . The overall response to progestins is ~25%.
- Single cytotoxic agents have been reported to achieve a response rate up to 40% in chemotherapy-naïve patients with metastatic endometrial cancer. Among those, platinum compounds, anthracyclines and taxanes are most commonly used alone and in combination.
- In non-randomized trials, paclitaxel with carboplatin or cisplatin demonstrated a response rate >60% and a possibly prolonged survival compared with historical experience with other non paclitaxel-containing regimens.
- In recurrent disease, only paclitaxel has consistently shown a response rate >20%. In a recently published study, the combination of weekly topotecan and docetaxel had clinical benefit and was well tolerated in heavily pretreated patients.

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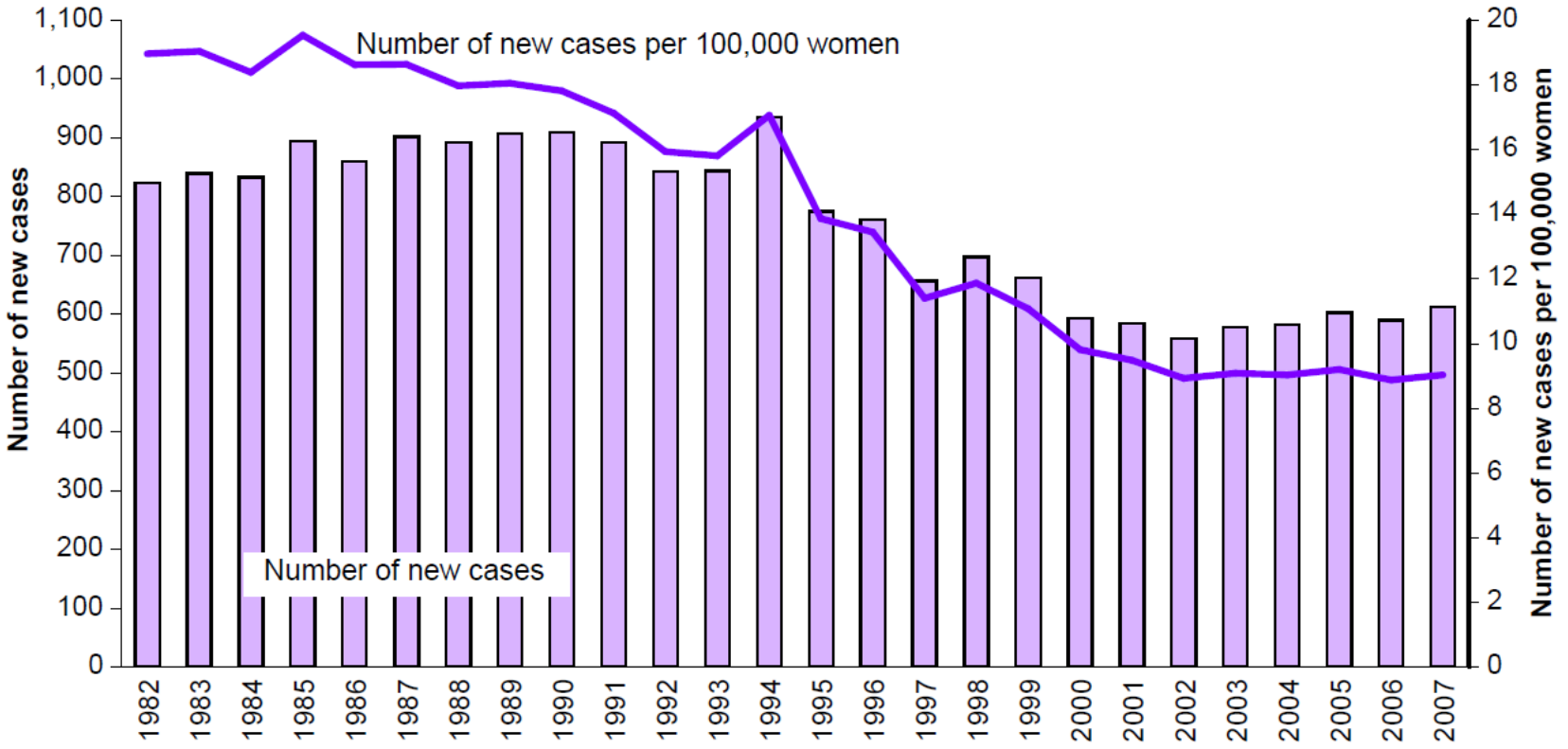
Cervical Cancer

Cervical Cancer Incidence



Note: The rates were age-standardised to the Australian population as at 30 June 2001.

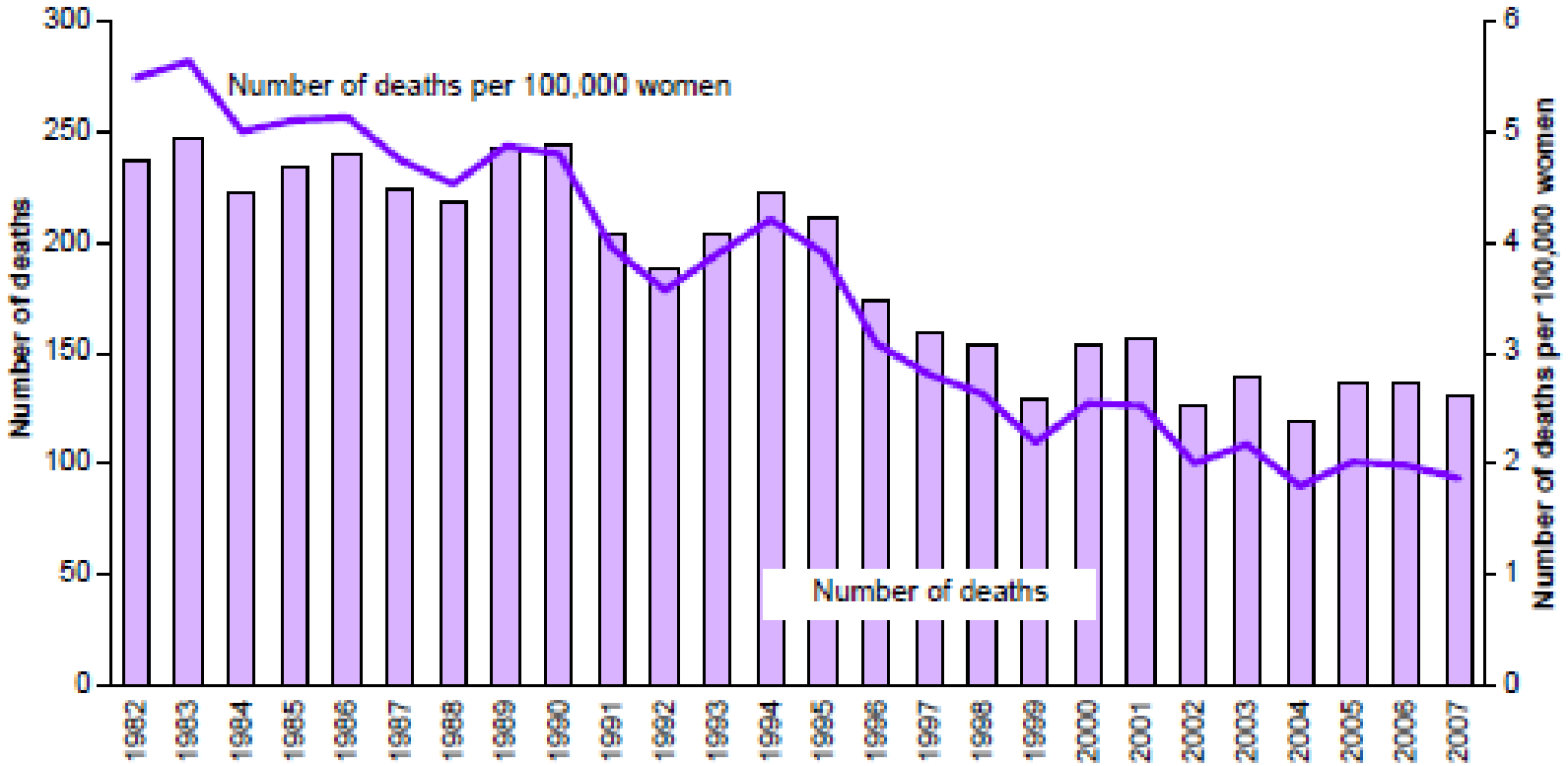
Source: AIHW Australian Cancer Database.

Figure 6.1: Incidence of cervical cancer, women aged 20–69 years, by year, 1982 to 2007

Cervical Cancer Mortality

- In 2007, deaths from cervical cancer comprised 1.2% of all cancer deaths in women, with a mean age of death of 62.6 years.
- Risk of dying from cervical cancer was 1 in 817 by age 75 years and 1 in 502 by age 85 years (AIHW & AACR 2010).

Cervical Cancer Mortality



Note: The rates were age-standardised to the Australian population as at 30 June 2001.

Source: AIHW National Mortality Database.

Figure 7.1: Mortality for cervical cancer, women aged 20–69 years, 1982 to 2007

Cervical Cancer Screening

- In the 2 years 2008–2009, there were 3,802,203 women in total who participated in the NCSP (that is, had at least one cervical cytology test over the 2-year period).
- This equates to 58.2% of eligible women, age-standardised to a participation rate of 58.6% for 2008–2009 to allow analysis of trends.
- The majority of cytology tests do not detect an abnormality—either squamous or endocervical in origin.
- In 2009, an abnormality (low-grade, high-grade or cancer) was detected in 5.4% of cytology tests. Of these, 74.8% were low-grade and 25.0% were high-grade, cancer making up the remainder

Cervical Cancer Staging

Stage 0	Carcinoma-in-situ
Stage I	Cancer confined to cervix
Stage II	Extension beyond cervix but not to pelvic wall
Stage III	Extension into pelvic wall
Stage IV	Extension beyond pelvis or invasion of bladder or rectum

Treatment – Stage I

- Conization: If the depth of invasion is less than 3 mm, no vascular or lymphatic channel invasion is noted, and the margins of the cone are negative, conization alone may be appropriate in patients wishing to preserve fertility.
- Modified radical hysterectomy: For patients with tumor invasion between 3 mm and 5 mm, radical hysterectomy with pelvic node dissection has been recommended because of a reported risk of lymph node metastasis of as much as 10%.
- Radical hysterectomy with node dissection: May also be considered for patients where the depth of tumor invasion was uncertain because of invasive tumor at the cone margins.
- Intracavitary radiation therapy alone: If the depth of invasion is less than 3 mm and no capillary lymphatic space invasion is noted, the frequency of lymph node involvement is sufficiently low that external-beam radiation therapy is not required. Radiation therapy should be reserved for women who are not surgical candidates.

Treatment – Stage II

- Either radiation therapy or radical hysterectomy results in cure rates of 75% to 80%.
- The selection of either option depends on patient factors and local expertise.
- A randomized trial reported identical 5-year overall survival (OS) and disease-free survival rates when radiation therapy was compared to radical hysterectomy.
- After surgical staging, patients found to have small volume para-aortic nodal disease and controllable pelvic disease may be cured with pelvic and para-aortic radiation therapy.
- The resection of macroscopically involved pelvic nodes may improve rates of local control with postoperative radiation therapy.
- Five randomized phase III trials have shown an OS advantage for cisplatin-based therapy given concurrently with radiation therapy.

Treatment – Stage III/IVA

- Intracavitary radiation
- EBRT to the pelvis combined with cisplatin or cisplatin/fluorouracil

Treatment – Stage IVB

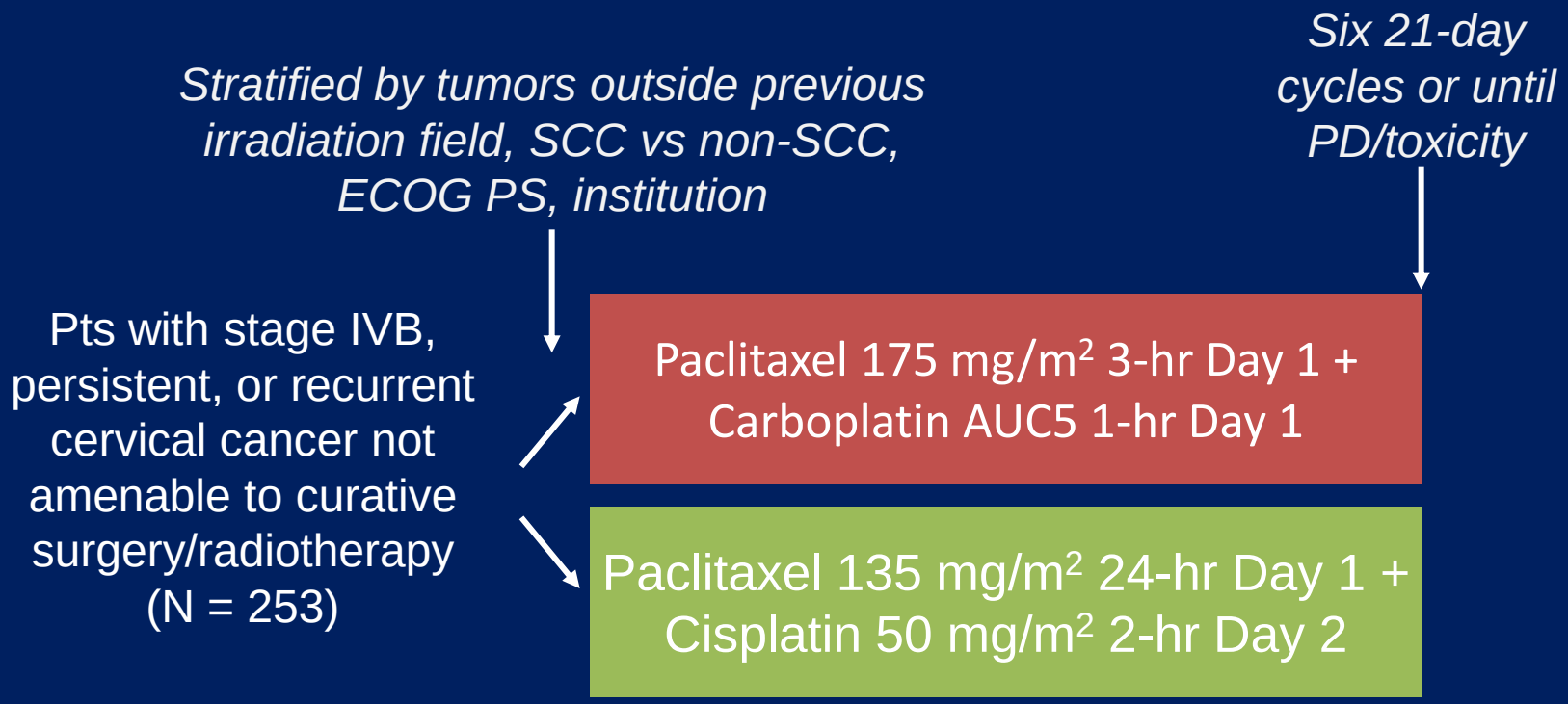
- No standard chemotherapy treatment is available for patients.
- These patients are appropriate candidates for clinical trials.
- Radiation therapy may be used to palliate central disease or distant metastases.
- Chemotherapy - Tested drugs include the following:
  - Cisplatin (15%–25% response rate)
  - Ifosfamide (31% response rate)
  - Paclitaxel (17% response rate)
  - Ifosfamide-cisplatin
  - Irinotecan (21% response rate in patients previously treated with chemotherapy)
  - Paclitaxel/cisplatin (46% response rate)
  - Cisplatin/gemcitabine (41% response rate)
  - Cisplatin/topotecan (27% response rate)

Prognosis – 5-yr Survival

Stage I	85-90%
Stage II	50-65%
Stage III	25-30%
Stage IV	< 15%

JCOG 0505: TC or TP for Advanced Cervical Cancer

- Randomized, phase III trial



Kitagawa R, et al. ASCO 2012. Abstract 5006.

JCOG 0505: Baseline Characteristics

Characteristic	TC (n = 126)	TP (n = 127)
Median age, yrs (range)	53 (22-72)	53 (29-74)
ECOG PS 0, %	76	77
Histology, % ▪Squamous ▪Adenosquamous ▪Adenocarcinoma	 83 3 13	 83 2 14
Disease status, % ▪Stage IVB or persistent ▪First recurrent ▪Second recurrent	 19 67 13	 21 65 14
Tumors present outside previous radiation field, %	60	64
Previous platinum CT, %	57	48
PFI, % ▪< 6 mos ▪≥ 6 mos < 12 mos ▪≥ 12 mos	 10 19 28	 16 16 17

Kitagawa R, et al. ASCO 2012. Abstract 5006. Reproduced with permission.

JCOG 0505: Results

Outcome	TC (n = 121)	TP (n = 123)	HR (95% CI)	*P* Value†
Median OS,* mos	17.5	18.3	0.99 (0.79-1.25)	.032
▪ No previous platinum (n = 117)	13.0	23.2	1.57 (1.06-2.32)	.838
▪ Previous platinum (n = 127)	19.0	16.3	0.69 (0.47-1.02)	.0008
Median PFS, mos	6.2	6.9	1.04 (0.80-1.35)	.053

*Primary endpoint. †Noninferiority 1-sided *P* value.

- TP significantly improves OS vs TC in pts with no previous platinum
- Predictable toxicities in both arms:
  - TP associated with more neutropenia, febrile neutropenia, creatinine elevation, nausea/vomiting
  - TC associated with more arthralgia, myalgia and neuropathy, but higher proportion of nonhospitalization periods (62% vs 46%; *P* < .0001)

Kitagawa R, et al. ASCO 2012. Abstract 5006.