Ovarian cancer

with update from ASCO 2013

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ONCOLOGY REGISTRAR

Epidemiology

- 225000 new incidence annually worldwide. Incidence stable since 1970s
  - 1600 new cases in Australia in 2010
- Median age at diagnosis 63
- Fourth commonest cause of cancer death in women in developed countries
- >60% of women diagnosed with Stage III/IV
  - symptoms of abdo pain, bloating, distension, constipation, back pain usually happen in advanced stage
- To date, no mortality benefit demonstrated with CA125 and TVUS screening.

Stage at diagnosis and 5-yr survival

		Stage at diagnosis	5-yr OS
Stage I	**Confined to the Ovary**	**20%**	**85%**
I_A	Growth limited to one ovary, no ascites, capsule intact, no surface tumor extension		
I_B	Same as I_A but involves both ovaries		
I_C	I_A or I_B but with positive washings or ruptured capsule		
Stage II	**Extends to True Pelvis**	**5%**	**60%**
II_A	Involves fallopian tube or uterus		
II_B	Extension to other pelvic tissues		
II_C	Either II_A or II_B but with positive washings or ruptured capsule		
Stage III	**Extends Beyond the True Pelvis**	**58%**	**26%**
III_A	Tumor limited to true pelvis but microscopic positive biopsy outside the pelvis		
III_B	Abdominal implants up to 2 cm		
III_C	Positive lymph nodes or abdominal implants > 2 cm		
Stage IV	**Distant Disease**	**17%**	**12%**

Subtypes

- Epithelial
  - High grade serous 75%
  - Mucinous 10%
  - Endometrioid 10%
  - Clear cell
  - Low grade serous
- Germ cell/small cell/Krukenberg

Ovarian Cancer Risk Factors

- 50 years of age or older
- Familial factors
  - Family history of breast, ovarian, or colon cancer ?3x baseline risk
  - Personal history of breast or colon cancer
  - Familial cancer syndrome (10%)
    - 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
  - First pregnancy at older than 30 years of age
  - Infertility, endometriosis
  - (fertility Rx does not increase risk)

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

Lifetime Risk of Cancers Associated With Specific Genes

Cancer, %	BRCA1	BRCA2	MMR*
Breast	35-60	30-55	0
Ovarian	35-45	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 (2% chance of BRCA)
- Male breast cancer

Natural History

- Precise natural history is poorly understood
- There is no direct evidence for a premalignant lesion in ovarian cancer.
- The entire peritoneum is at risk because peritoneal carcinomatosis may develop after an oophorectomy

Ovarian Ca Screening for general population: PLCO trial

- 68557 participants 55-74yo w/o prior hx of oophorectomy
- annual Ca125 for 6 years and TVUS for 4 years in intervention grp
- Median f/u:12.4 years
- Results:
  - Similar detection rate (5.7 v 4.7 per 10000 person-yrs), HR 1.21 CI:0.99-1.48
  - <60% of ovarian ca detected were high grade serous subtype.
  - No difference in ovarian ca mortality (3.1 v 2.6 per 10000 person-years) HR 1.18 CI:0.82-1.71.
  - Harm from false-positive screen: 3285 cases with 15% major complication rate from surgical intervention!

JAMA 2011:305 (22):2295-2303

Ovarian Ca screening in 'high risk grp'

- UKFOCCS Phase 1: annual Ca125 and TVUS
  - Sensitivity >80%, NPV 99%, PPV 25% (ie 4 operations for 1 case of ca)
  - Only 30% of screen detected ca were stage 1-2
  - 89% of screen detected ca were in BRCA carriers.
  - Only 4/2960 cases of screen detected ca in women with +FH!
- UKFOCCS Phase 2: 4mthly Ca125 and annual TVUS plus ROCA (change in algorithmic scale of Ca125)
  - Breast or ovarian ca family, BRCA?proportion, HNPCC or Ashkenazi
  - 4531 women median age 45 (35-84), only 1/3 >50yo
  - sens: 75% (or lower!) spec 96% PPV 13%
  - 12 cases of screen-detected cancer, with 42% of cases in stage 1/2
  - 11/12 underwent optimal cytoreduction (does not translate to cure)
  - 14.4% underwent RRSO, 3.3% underwent RRSO due to false+, 4/653 had incidental ca (? Even higher number if proper serial sectioning method)

JCO 2013;31:49-57
ASCO 2013 abstr 5502

Ovarian Ca screening

- Major organisations do not recommend ovarian cancer screening:
  - Poor understanding of natural history
  - Poor performance of current test in detecting early stage disease
  - No survival benefit demonstrated even in 'high risk grp"
  - Potential for harm
- RRBSO remains the standard of care for BRCA carriers and reduces risk of OC by 75-96%
- Current estimated uptake of RRBSO in BRCA carriers by countries:
  - Australia 38%
  - UK 40%
  - France 70%
  - Canada 57%

Management of Ovarian Cancer

SURGICAL STAGING AND DEBULKING

Initial Surgical management

- Surgery is usually performed upfront regardless of stage:
  - Obtain tissue diagnosis
  - Perform surgical staging
  - Optimal debulking of tumour: improves response to chemo, decreases disease related symptoms and potentially improves immune response
- Exception: poor ECOG, disease 'too bulky' or other primary not able to be excluded. Consider neoadjuvant chemotherapy
- Engage experienced gynaeonc surgeon for optimal primary debulking (GOG: <1cm residual disease, but ?less is even better)
- Minimal benefit in interval debulking after 'suboptimal primary debulking'
  - Benefit mainly lies with pts who received poor surgery upfront. EORTC v GOG152 trial

Steps in Surgical Staging

1. Obtain any free fluid for cytologic evaluation

2. If no free fluid is present, obtain washings by instilling saline and recovering the fluid. The fluid should irrigate the cul de sac, paracolic gutters, and area beneath each diaphragm.

3. Systematically explore all intraabdominal organs and surfaces: bowel, liver, gallbladder, diaphragms, mesentery, omentum, and the entire peritoneum should be visualized and palpated, as indicated

4. Suspicious areas or adhesions should be biopsied. If there are no suspicious areas, multiple biopsies should be obtained from the peritoneum of the cul-de-sac, paracolic gutters, bladder, and intestinal mesentery when the disease appears confined to the ovary. These biopsies are not needed if the patient has advanced disease.

5. The diaphragm should be biopsied or scraped for cytology. A laparoscope and biopsy instrument may be used.

6. The omentum should be resected from the transverse colon.

7. The retroperitoneum should be explored to evaluate pelvic nodes. Suspicious nodes should be removed and sent for frozen section examination.

8. The paraaortic nodes should be exposed and enlarged nodes removed. Nodes superior to the inferior mesenteric artery should also be resected.

9. In the absence of suspicious nodes, pelvic and paraaortic nodes should still be sampled to exclude the possibility of microscopic stage III disease.

10. A total abdominal hysterectomy and bilateral salpingo-ophorectomy is performed. (Fertility-conserving surgery may be an option for some women).

Impact of residual tumor on survival in advanced ovarian cancer

Study	Year	Survival (months)	
		Optimal debulking (definition)	Suboptimal debulking
Hacker NF	1983	18 (0.5 to 1.5 cm)	6 (>1.5 cm)
		40 (<0.5 cm)	
Vogl SE	1983	40+ (≤2 cm)	16 (>2 cm)
Delgado G	1984	45 (<2 cm)	16 (>2 cm)
Pohl R	1984	45 (<2 cm)	16 (>2 cm)
Conte P	1985	25+ (<2 cm)	14 (>2 cm)
Posada JG	1985	30+ (<2 cm)	18 (>2 cm)
Louie KG	1986	24 (<2 cm)	15 (≥2 cm)
Hainsworth J	1988	72 (≤3 cm)	21 (>3 cm)
Piver MS	1988	48 (≤1 cm)	21 (>1 cm)
Sutton GP	1989	45 (<3 cm)	23 (≥3 cm)
Munkarah AR	1997	25 (≤2 cm)	15 (>2 cm)
Bristow RE	1999	38 (≤1 cm)	10 (>1 cm)
Zang RY	2000	19 (≤1 cm)	8 (>1 cm)

Modified from Ozols, et al. Epithelial ovarian cancer. In: Principles and Practice of Gynecologic Oncology, 3rd edition, Hoskins WJ, et al (Eds), Lippincott, Williams & Wilkins, Philadelphia 2000. p.1005.

References:

Stage I And II OC: role of adjuvant chemotherapy

- 8% 5 year improvement in OS was shown from a metaanalyses of 13 trials in stage 1 disease. However 90% of pts did not receive proper surgical staging/lymph node sampling.
- Another metaanalyses showed adjuvant chemo significantly improved PFS and OS
  - Subgrp analyses showed benefit only in early stage disease that was incompletely resected
  - One trial showed benefit only in high risk disease.
- ACTION trial showed improvement in RFS but only trend towards OS benefit. In pts who had complete surgical staging, there was no RFS or OS benefit

Adjuvant Rx for early stage Ovarian Ca

- NCCN guideline suggests adjuvant chemo in stage 1C or stage II, clear cell OC (any stage), and grade 3 OC
- No consensus on optimal chemotherapy agent and duration of treatment:
  - ?carboplatin and paclitaxel
  - 3 cycles vs 6 cycles of adjuvant Rx: GOG 157 showed non-significant trend towards less relapse but similar OS and more toxicity with 6 cycles.

Postop Management of advanced ovarian cancer

Standard: ?Carbo AUC6 + Pacli

- GOG 111 and OV10: Cisp/Paclitaxel v Cisp/Cyclo showed 11% ARR favouring taxane NEJM 1996;334(1):1-6, JNCI 2000;92(9):699-708.
- Carboplatin is at least as effective as Cisplatin Ann Oncol 1999;10 supp1:35-41
- SCOTROC: Docetaxel is as effective as Paclitaxel but more myelosuppressive

  JNCI 2004;96(22):1682
- No additional benefit of continuing chemo beyond 6 cycles.
- 2006 metaanalysis of 60 trials with 15609 women:
  - Platinum monotherapy v Platinum-based combi: HR 1.16 CI:0.86-1.58)
  - Platinum-non taxane v Platinum-taxane: HR 1.28 CI:1.07-1.53)

Improving outcome beyond Carbo/Paclitaxel

- First line Carbo/Paclitaxel showed RR 70-80% with more than 50% achieving CR after optimal cytoreduction
- However, up to 70% relapse within 1-3 years.

Better schedule for Carbo/Pacli

- JCOG 3016 trial Lancet 2009;374:1331-1338
  - 637 pts stage II to IV (65% SIII, 15% SIV)
  - Carbo AUC6 + Pacli180mg/m2 D1 q3/52 v Carbo AUC6 D1 + Pacli 80mg/m2 D1,8,15 q3/52
  - Improved PFS 17.2m v 28m HR 0.71 CI: 0.58-0.88
  - Improved 3-yr OS 65.1% v 72.1% HR 0.75 CI 0.57-0.98
  - Improved OS at 6.4-yr fu: 62m v not reached HR 0.79 CI 0.63-0.99 (ASCO 2012)
  - Greater toxicity with dose dense strategy:
    - Neutropenia 88% v 92%, G3 or 4 anaemia 44% v 69%, Less treatment completion 61% v 73%
    - Similar rate of neurotox and febrile neut (9%)

Better carbo/taxol schedule

- MITO-7 JCO 2013;31 suppl;abstr LBA5501
  - 822 pts stage IC to IV (66% SIII, 18% SIV)
  - Carbo AUC2 +Pacli 80mg/m2 both D1,8,15 q3/52 v C AUC6+P 180mg/m2 q3/52 v
  - 20m f/u: Similar PFS (18.8m v 16.5m HR 0.88 CI 0.72-1.06). OS immature
  - Better tolerated with less neuropathy (6% v16%), neutropenia, renal dysfunction (0% v 2%). Better QOL
- Upcoming trials: ICON-8

ADDING THIRD CYTOTOXIC

- Rationale: addition of non-cross resistant drug to platinum/paclitaxel combi may improve OS
- Multiple trials. Biggest is GOG182-ICON5: JCO 2009;27(9):1419-1425
  - 5 arms study of adding either Gemcitabine, Topotecan or Caelyx to backbone of Carbo/pacli
  - Study closed after 4312 pts accrued due to no PFS and OS benefit over CP

Role of targeted agents: pazopanib

- AGO-OVAR16:
  - Pazopanib (24m) v placebo in pts who do not have progression after surgery and completion of >4 cycles of platinum-taxane chemo (940pts, FIGO II-IV, 85% in CR at entry). Improved PFS from 12.3m to 17.9m. OS immature

    ASCO 2013. JCO 2013;31 sup:abstr LBA5503

Role of Bevacizumab

- GOG 218: carbo/paclitaxel v CP+Bev 15mg/kg v CP+Bev->Bev 12m maintenance only managed to show improved PFS from 10.3m to 11.2m to 14.1m. 2.3% risk of GI perf. No OS benefit: 39m in both arms. Note: crossover to Bev allowed at progression.
- ICON-7: carbo/pacli v carbo/pacli+Bev Bev 36 wks at 7.5mg/kg Bev. Include 9% high risk stage early stage. Improved PFS at 42m (22m v 24m) but no difference in OS. In pts at high risk of progression (stage IV or stage III or residual tumour >1cm) there is improved PFS 14m v 18m, and OS 29m v 37m (posthoc analysis). 2013 QOL update showed no benefit with addition of Bev. Final OS pending
- BOOST will re-examine 15m v 30m of Bev (if we believe final OS data from ICON-7

Role of intraperitoneal chemotherapy

- Rationale: direct delivery of drug into peritoneal cavity increase the dose intensity without increasing plasma drug levels and potentially decrease systemic SEs. Only use in optimally debulked pts
- GOG104:
  - IV Cyclo +IV or IP Cisp100mg/m2 q3/52.
  - Improved OS with IP group 49m v 41m but at the cost of abdominal pain
- GOG114:
  - 6 cycles IV Cisp 75mg/m2+Pacli135mg/m2 q3/52 v 2 cycles of IV Carbo AUC9 q4/52 followed by 6 cycles of IP Cisp 100mg/m2+IV Paclitaxel 135mg/m2 q3/52
  - Improved OS with IP 63m v 52m, but only 18% received >2 IP cycles
- GOG172:
  - IV Cisp 75mg/m2 +Pacli 135mg/m2 q3/52 v IV Pacli 135mg/m2+ IP Cisp 100mg/m2 + IP pacli 60mg/m2 d8
  - Improved OS with IP 65.6m v 49.7m. More haem toxicities
  - ?benefit from additional dose of paclitaxel
- Poor uptake: concern re tox and logistics issues

Neoadjuvant chemotherapy

- Consider in women with extensive disease *and poor ECOG*. No consensus on who should receive NACT. ?all pts need preop laporoscopy for diagnostic and staging
- Advantage in responders: less extensive surgery and less morbidity from surgery
- EORTC 55971 Gynecol Oncol 2010;119(1):1-3
  - 670 pts w potentially operable stage III and IV ovarian ca
  - Primary debulking surgery, then 6 cycles of chemo or 3 cycles of neoadjuvant carbo/paclitaxel with interval debulking surgery, then more chemo.
  - Improved optimal debulking rate (residual <1cm) 41.6% v 80.6%. (*cw 75% optimal primary debulking rate in experienced centres)*
  - Less periop complications: death 0.7% v 2.5%, infection 2 v 8&, haemorrhage 4 v 7%
  - Similar PFS (12m) and (OS 29 v 30m). Pts who had primary surgery had improved OS if no residual disease (45 v 38m) or <1cm disease (32 v 27m)!
  - Nb: 3% did not have met ovarian ca at laparotomy! 25% did not receive standard C/P

Neoadjuvant chemo: MRC CHORUS

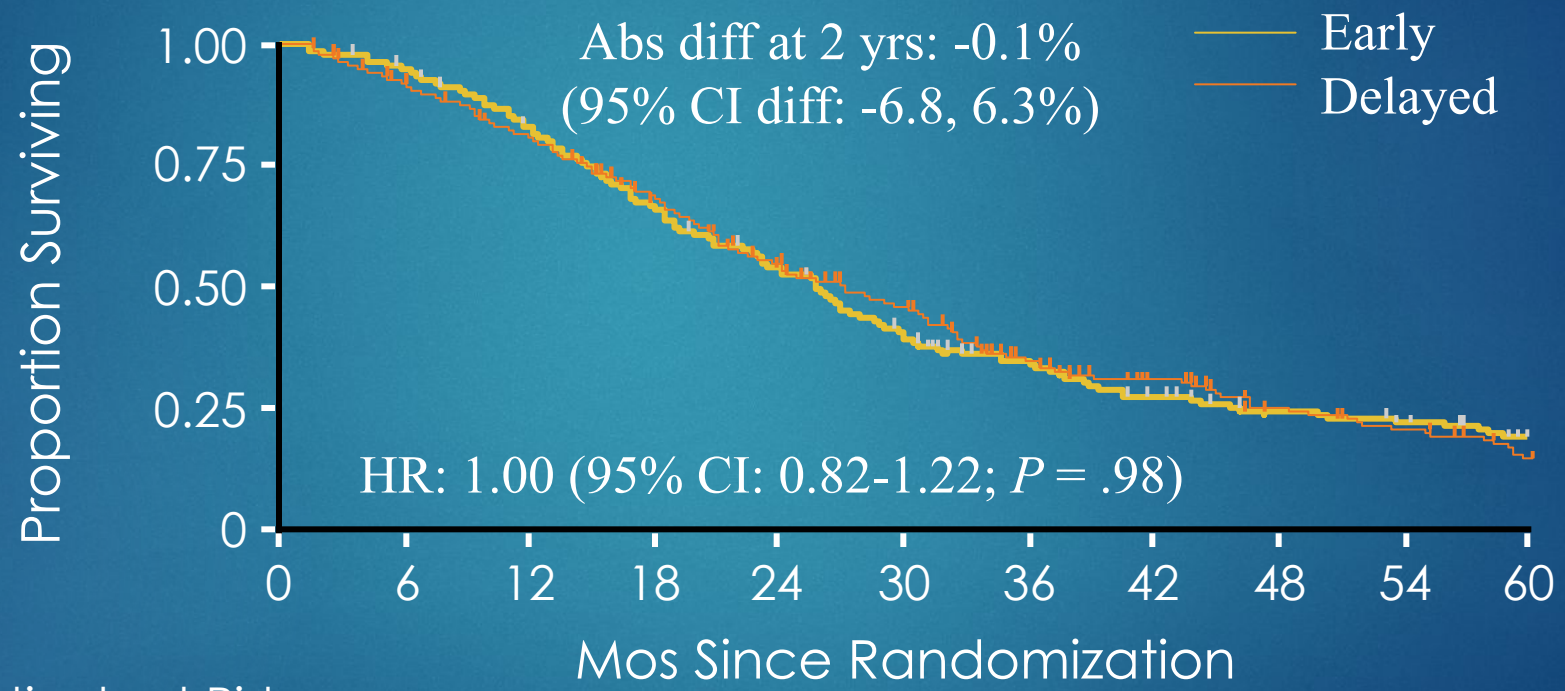
- 550 Pts stage III to IV. 72 centres in UK and 2 in NZ
- Non-inferiority trial with similar design to EORTC 55971
  - Exclude >6% decrease in 3-yr estimated OS of 50%
- Results: non-inferior PFS and OS
  - PFS: 11.3m v 10.7m
  - OS: 24.5m v 22.8m
- Less postop morbidity/mortality with NACT
  - G3 or 4 complications: 14% v 24%
  - D/c within 2/52: 92% v 74%
  - Death within 28 days: 5.6% v 0.5%
- Criticism of 'suboptimal surgery':
  - av duration of debulking surgery of 2 hrs,
  - Rate of residual disease >1cm in primary surgery arm of 61% v 25%
  - High rate of mortality
- Nonetheless, both EORTC and CHORUS showed similar results
- Neoadjuvant chemo is an alternative esp in women who are deemed unlikely to have residual microscopic disease post primary debulking.

Recurrent ovarian cancer

Current Questions in Recurrent Disease

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

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

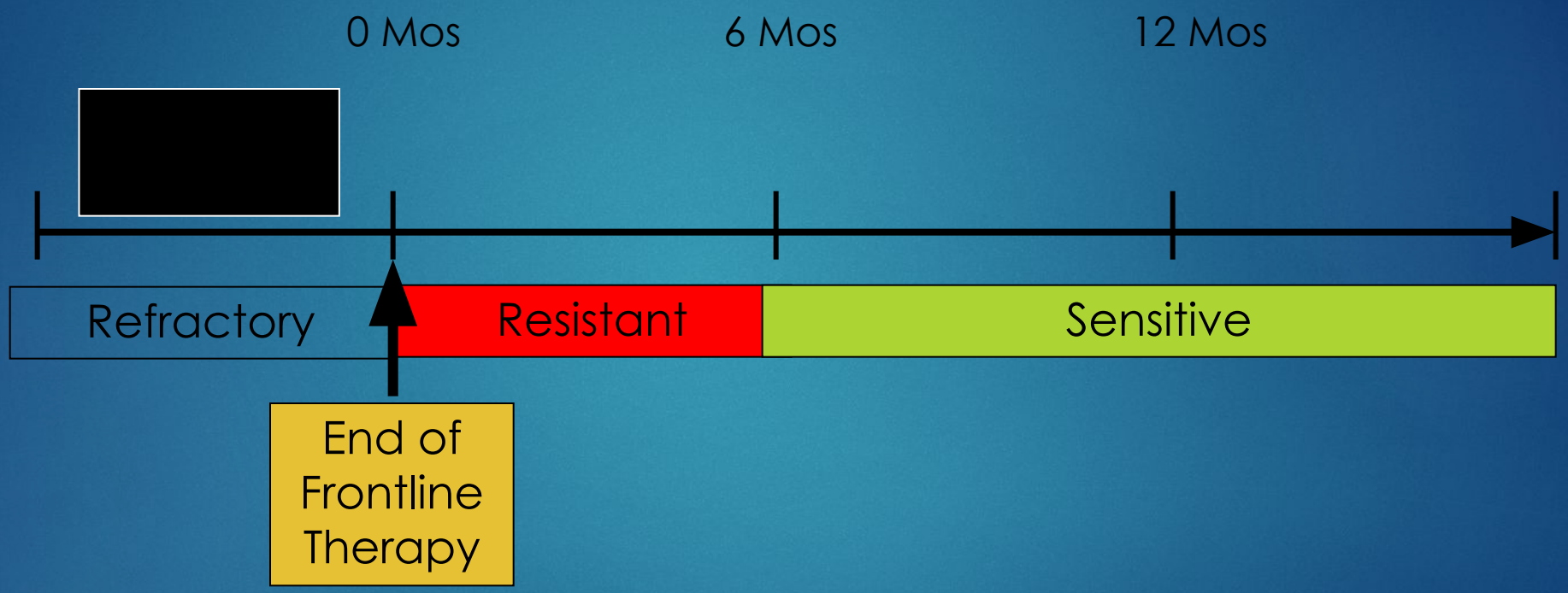
Pros

- 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

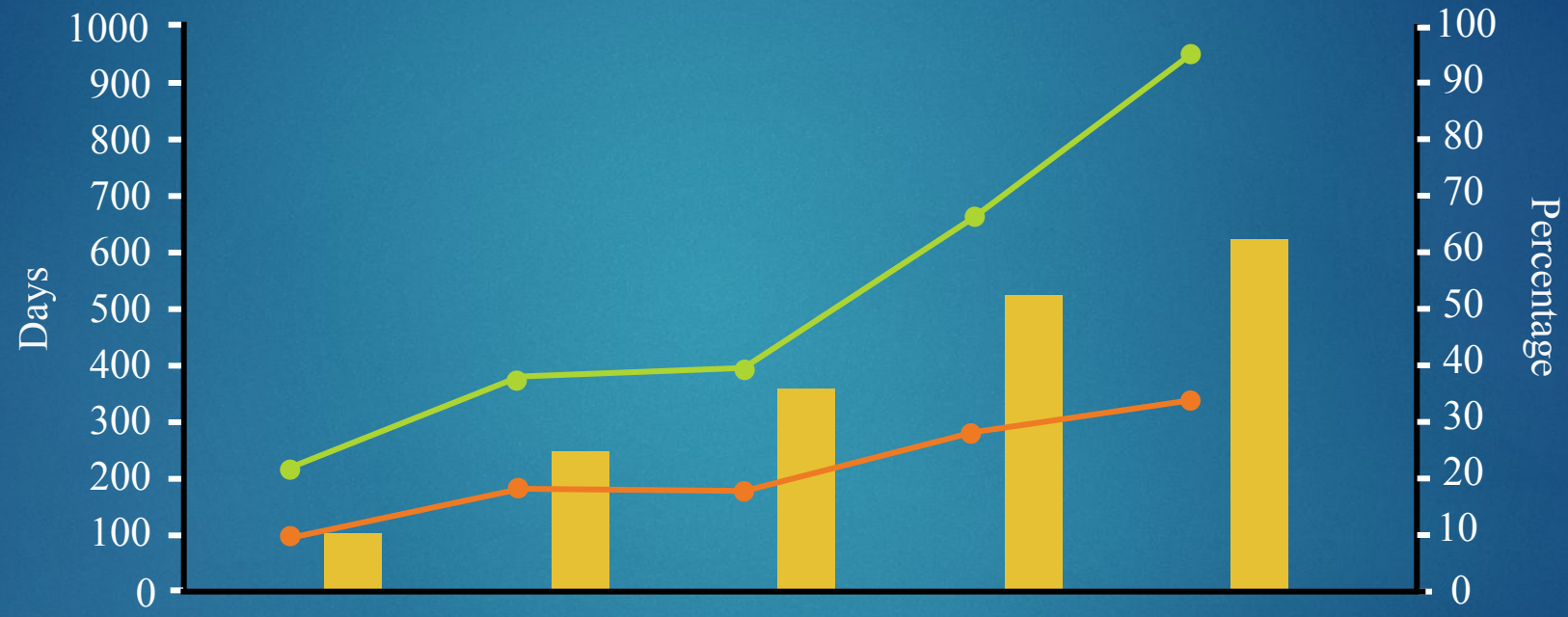
Cons

- 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



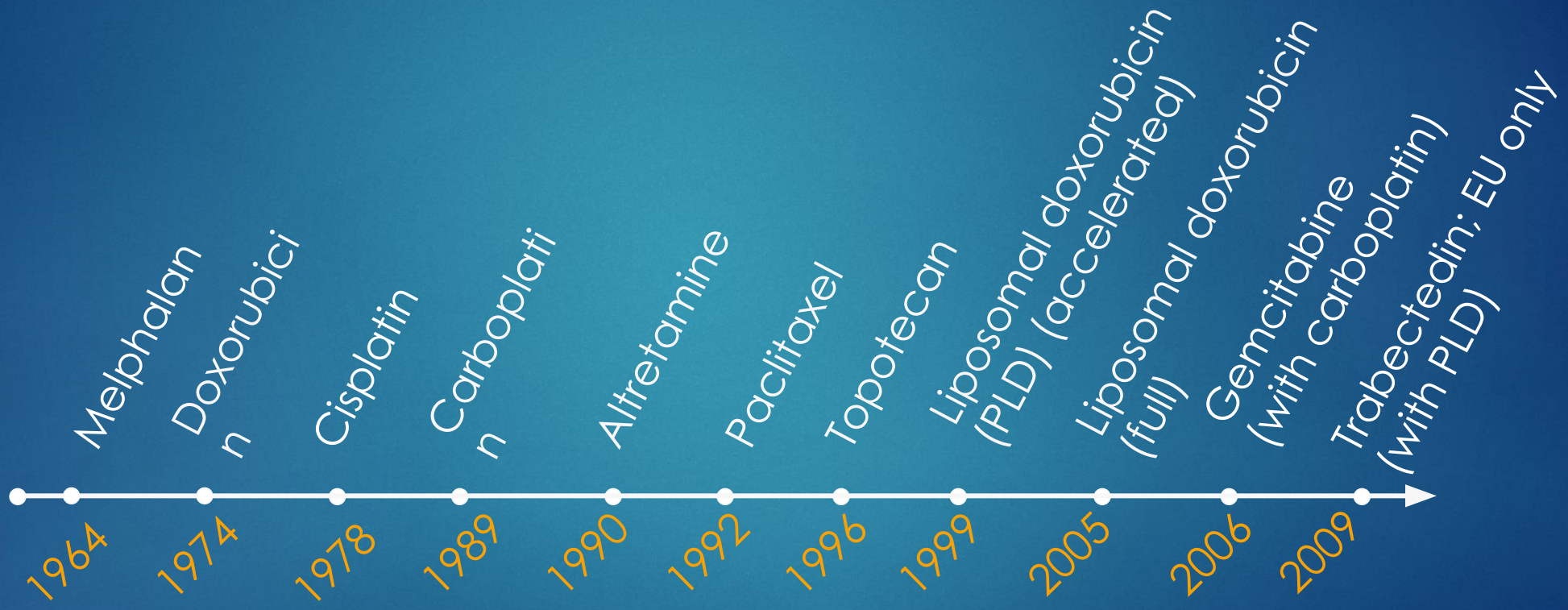
Recurrent Ovarian Cancer: Effect of Platinum-Free Interval and Survival



	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



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

Recurrent Ovarian Cancer

- ICON-4
- CALYPSO:
- Intergroup
- OCEANS: CarboAUC4/Gem (up to 10 cycles)+/-Bev 15mg/kg in platinum sensitive OC, followed by Bev maintenance. Improved PFS 8.4m v 12.4m, RR 57.4% v 78.5%. No OS benefit at second interim analysis! ?crossover 33.3m v 35.2m JCO 2012;17:2039-2045