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13th EDITION
2016 CAGPO ANNUAL MEETING
SEPTEMBER 29 – OCTOBER 2, 2016, FOUR SEASONS HOTEL VANCOUVER, BRITISH-COLUMBIA

Treatment Update on Ovarian Cancer - It's Not Just "Carbo-Taxol" Anymore

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October 1, 2016

Conflict of Interest

I have an affiliation with AstraZeneca.

- Funding for research (2016)
- Honoraria for advisory board attendance (2015).

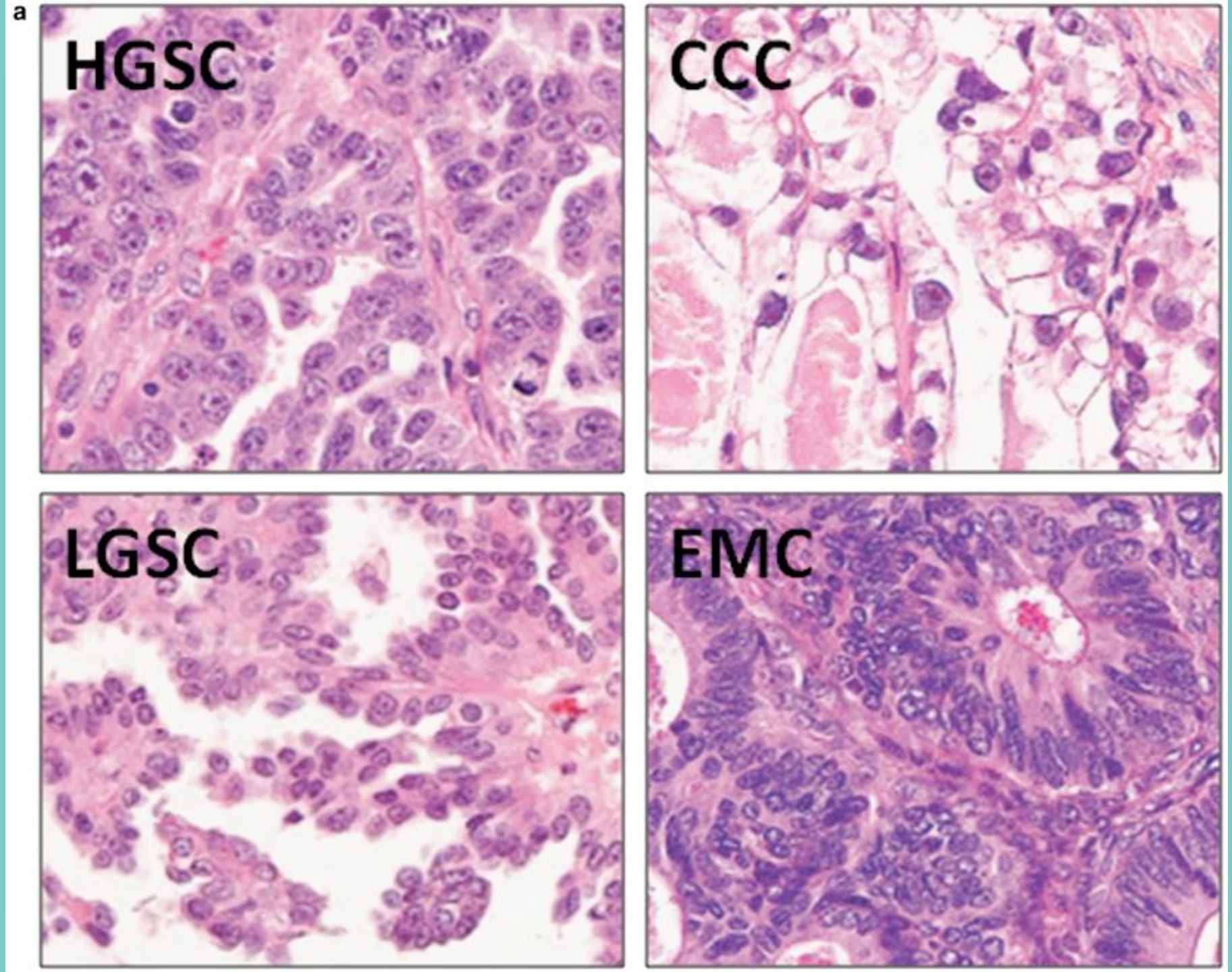
Overview

- Etiology/Origins of Ovarian Cancer
- Timing of Surgery
- Treatment of:
  - Newly diagnosed ovarian cancer
    - The role of IP therapy
    - The role of bevacizumab
  - Recurrent ovarian cancer – emerging role of PARP inhibitors
- Post Treatment Follow-Up
  - Value of CA-125

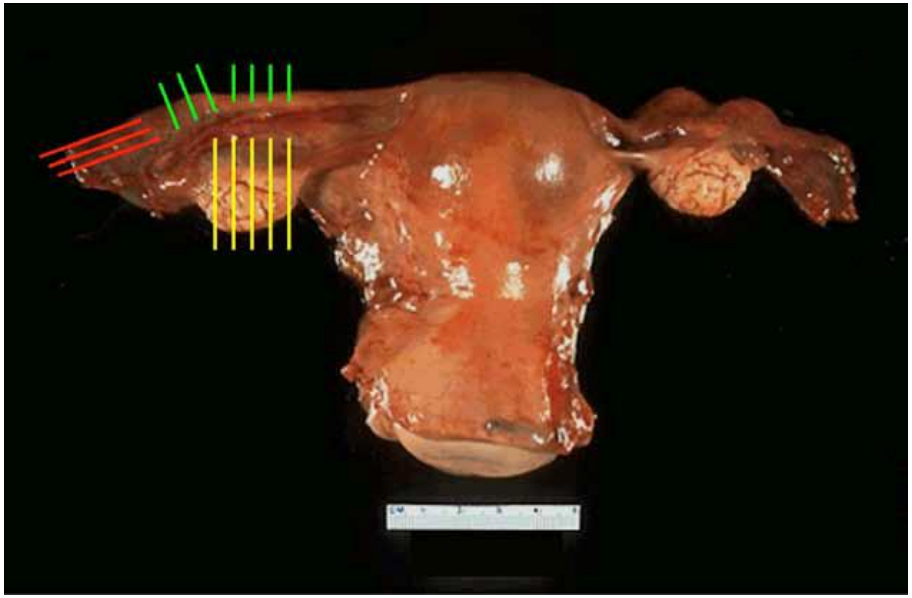
Etiology and Classification

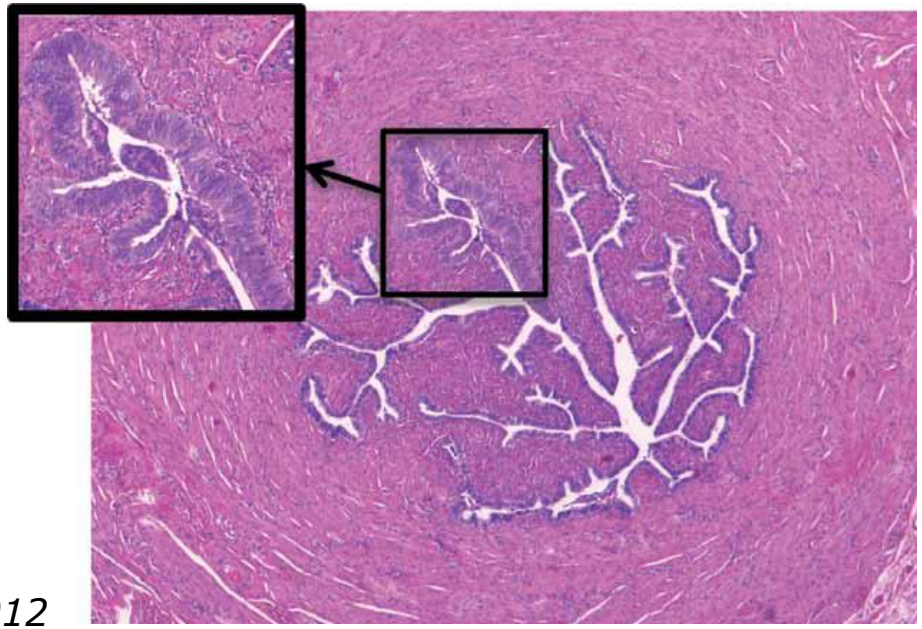
- Complexity of Ovarian Cancer long overlooked
- Used to believe that different histology = morphological variants
- What we have learned:
  - Histotype broadly defines different diseases
    - High grade serous
    - Clear Cell
    - Mucinous
    - Endometrioid
    - Low grade serous
    - Other very rare types…

Ovarian Cancer Etiology/Classification

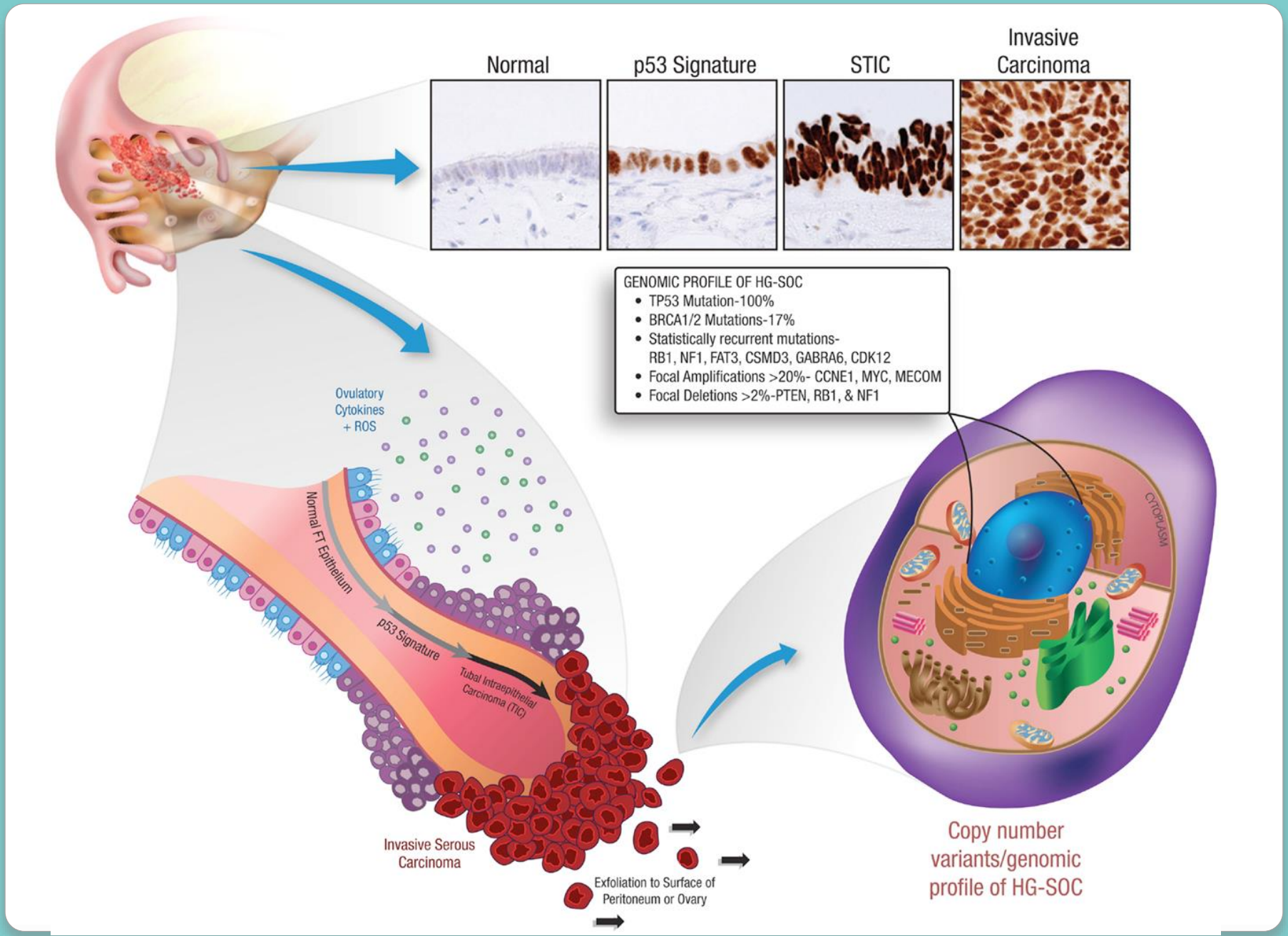

a
HGSC
CCC
LGSC
EMC

	HGSC	Clear Cell	Endometrioid	Mucinous	LGSC
Portion of cases	**70**	**12**	**11**	**3**	**3**
Genetic Risk Factors	BRCA1/2	HNPCC	HNPCC	none known	none known
Precursor Lesions/Cell of Origin	**STIC**, p53 signatures	**Endometriosis**	**Endometriosis**	not known	SBT
Common stage at presentation	advanced	early	early	early	advanced
Pattern of Spread	trans - coelomic	trans-coelomic/ hematogenous	????	pseudomyxoma pertonei/ hematogenous	transcoelomic
Response to Platinum-based therapy	chemo-sensitive	chemo-resistant, radiosensitive	chemo- sensitive	chemo -resistant	chemo-resistant
Molecular aberrations	p53, BRCA1, BRCA2, HR defects	PI3K, ARID1A, MSI	PTEN, bcatenin, ARID1A, MSI	KRAS, HER2	BRAF, KRAS, NRAS





Tone et al. Clin Adv Hem Onc 10;5:May 2012



Jones and Drapkin Front. Oncol., 26 August 2013 | http://dx.doi.org/10.3389/fonc.2013.00217

- **BRCA mutation carriers:**
  - Risk-reducing BSO
    - Isolated STIC 1-8%
      - Age dependence

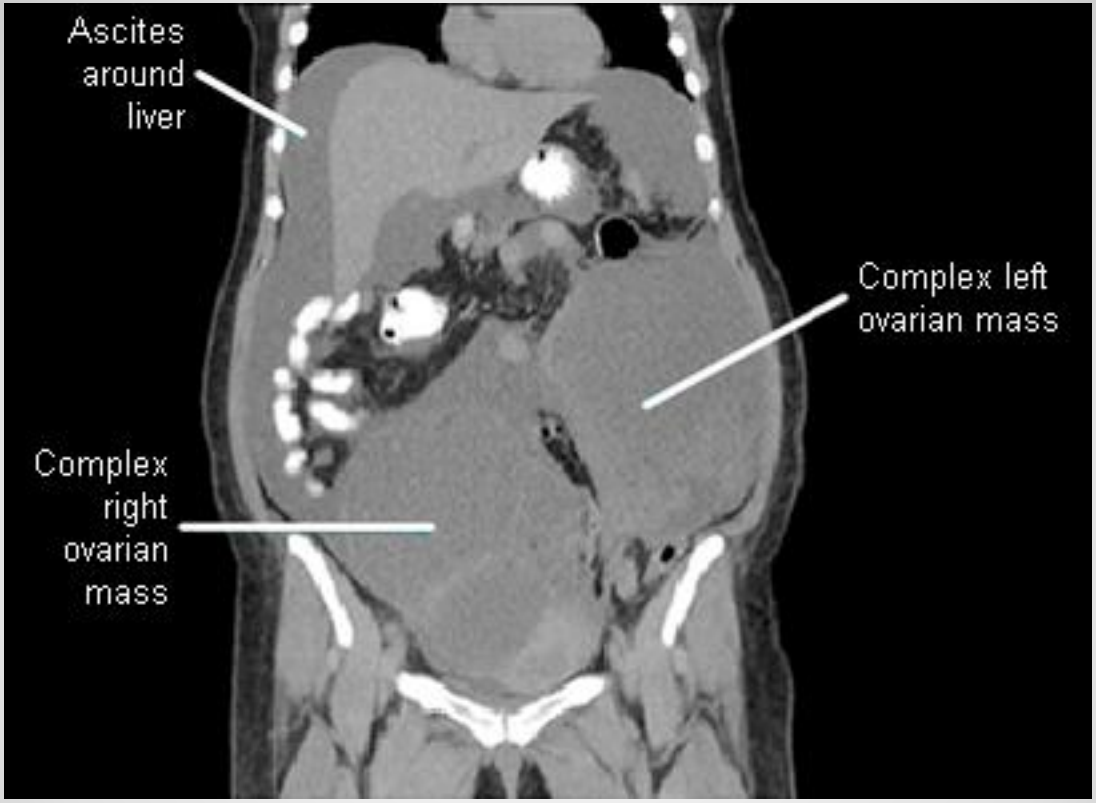
- **Low-Risk for Hereditary and Breast Cancer Syndrome:**
  - Unknown, but very low
    - Age dependence (lifetime risk of ovarian cancer is 1/70)

Early Detection of high grade tubal serous carcinoma in Women at low-risk for Hereditary Breast and Ovarian Cancer Syndrome….Rabban et al. Am J Pathology. 2014

STIC incidence

- Opportunistic Salpingectomies
- GOC (2011):
  - "Due to its cancer prevention potential, it is recommended that physicians discuss the risks and benefits of bilateral salpingectomy with patients undergoing hysterectomy or requesting permanent, irreversible contraception"
- American College of Obs & Gyn (2015)
  - Sectioning and Extensive Examining of the Fimbria

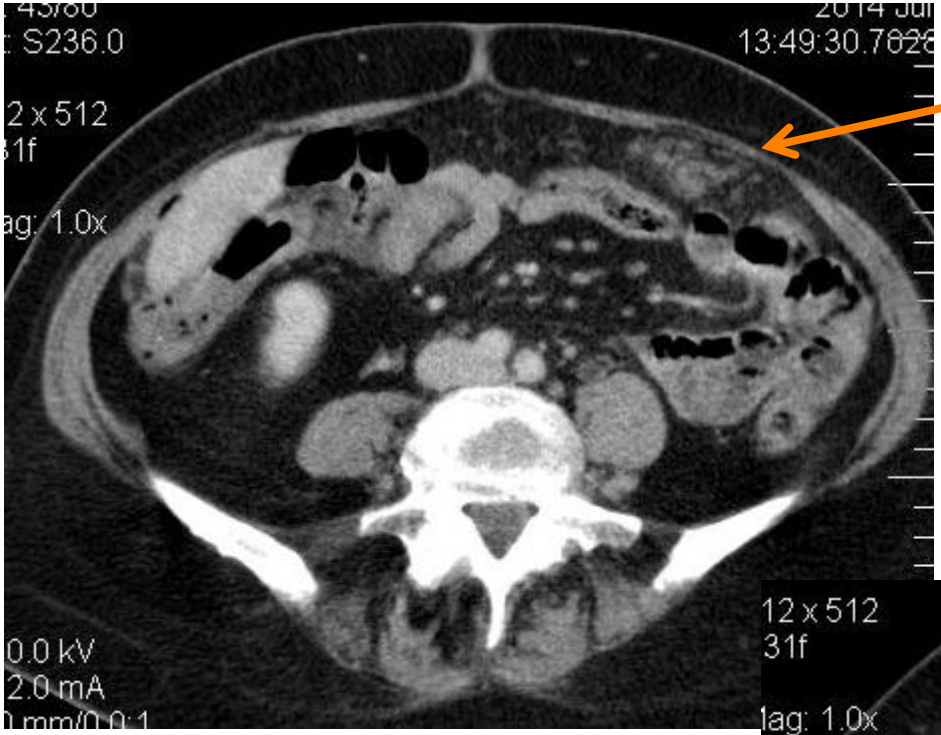
Opportunistic Salpingectomies



Timing of Surgery

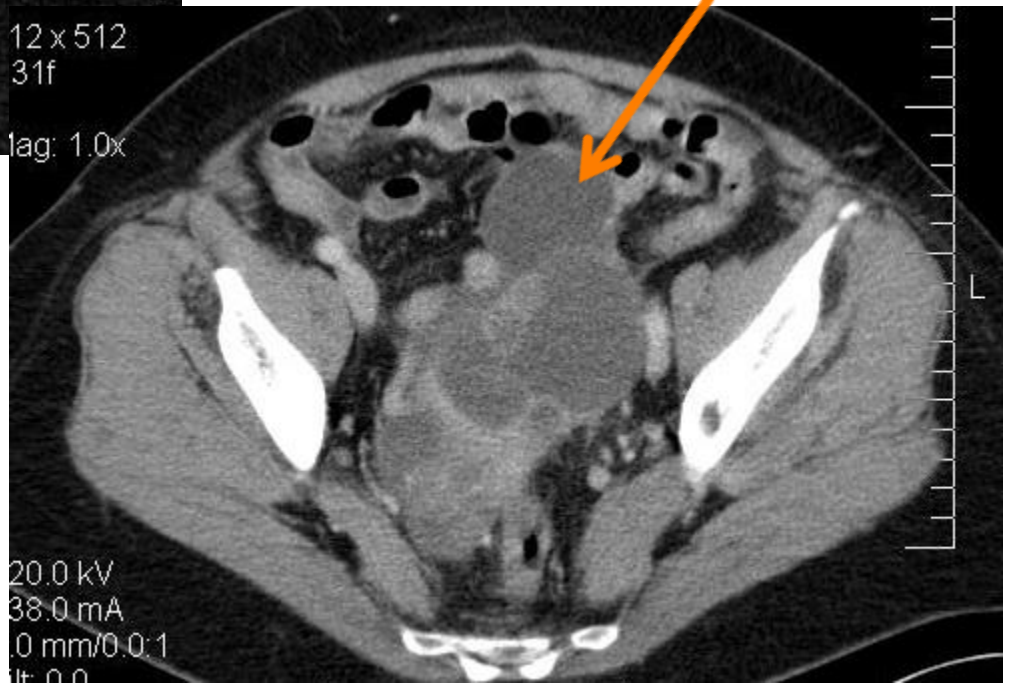
Surgery

- Suspected/Diagnosed Ovarian Cancer: requires review with a Gynecologic Oncologist!
- Usually suitable for surgery if:
  - Pelvic mass
  - Omental cake
  - All disease felt to be removable by a gynecologic oncologist
- Usually delay surgery if:
  - Diffuse peritoneal disease/disease under the diaphragms
  - Massive ascites
  - Large retroperitoneal LNs
  - Acute medical problem – MI/unstable angina, acture PE/DVT



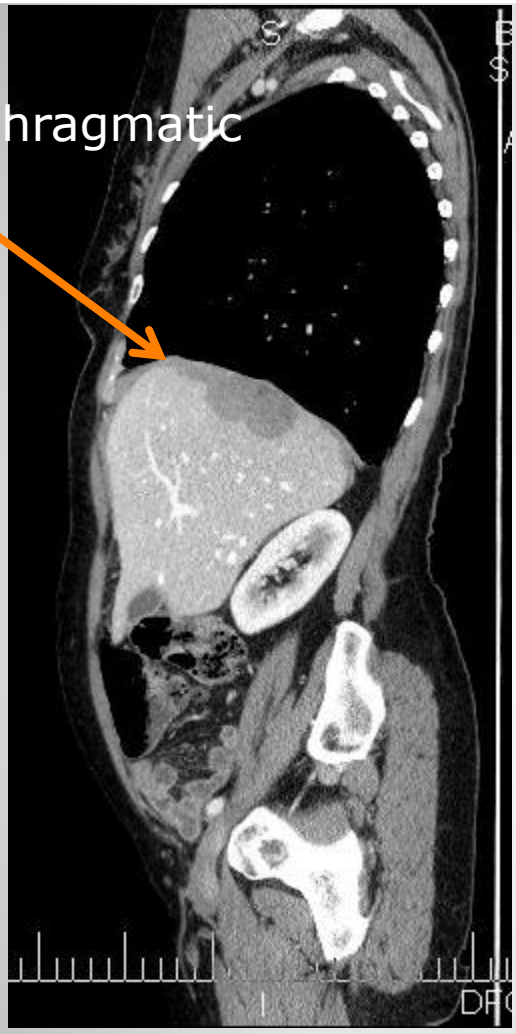
Omental mass

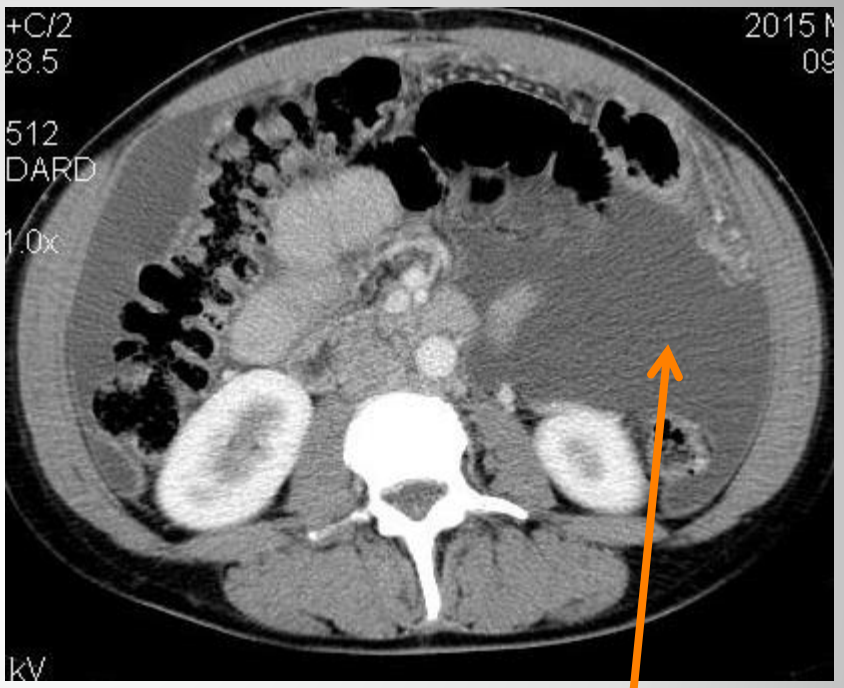
Pelvic Mass



This case had upfront surgery

Subdiaphragmatic disease





Massive ascites

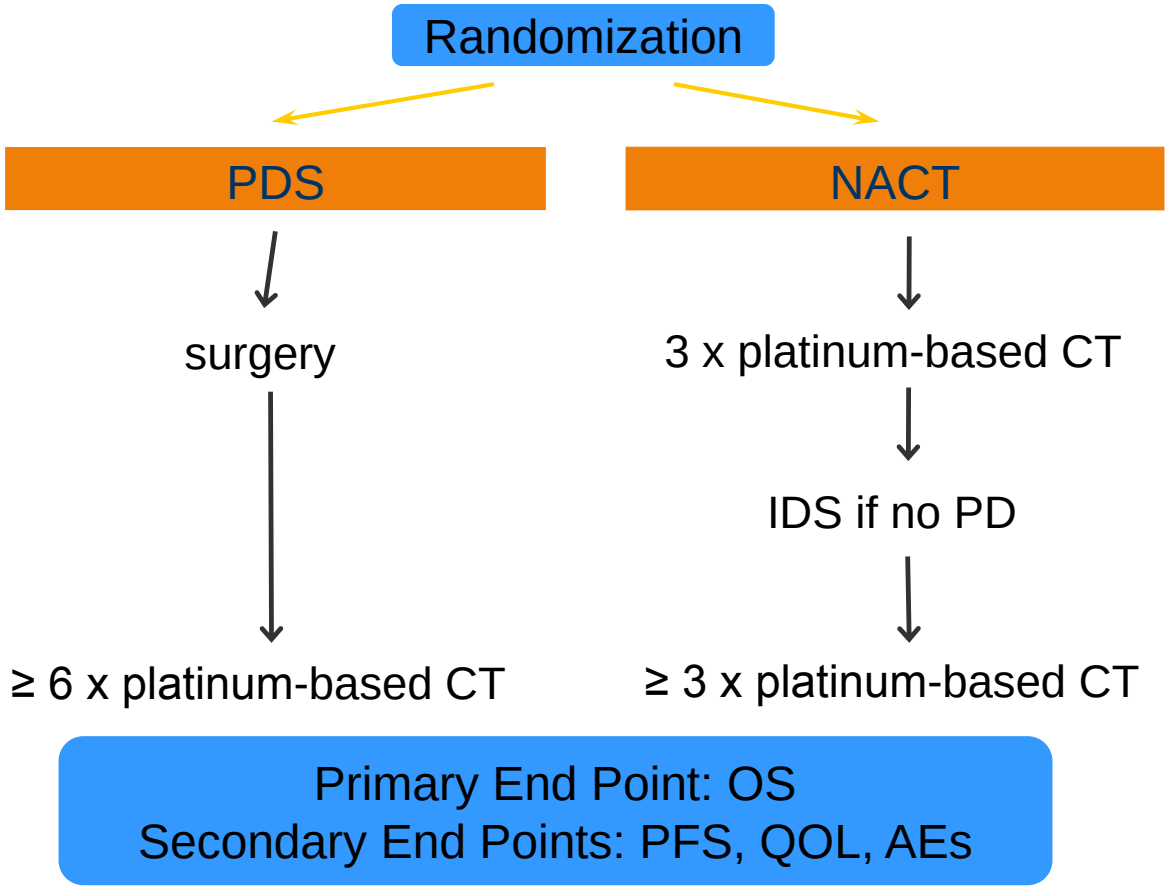
These cases had neoadjuvant chemotherapy

Timing of Surgery

- Two randomized phase III trials
- EORTC 55971 trial
- CHORUS
  - Pts with stage III or IV ovarian cancer
  - Otherwise fit for surgery (no PE/DVT, or serious commorbidity)
  - Outcomes are the same whether surgery first or chemo first.

NACT + IDS Vs. PDS

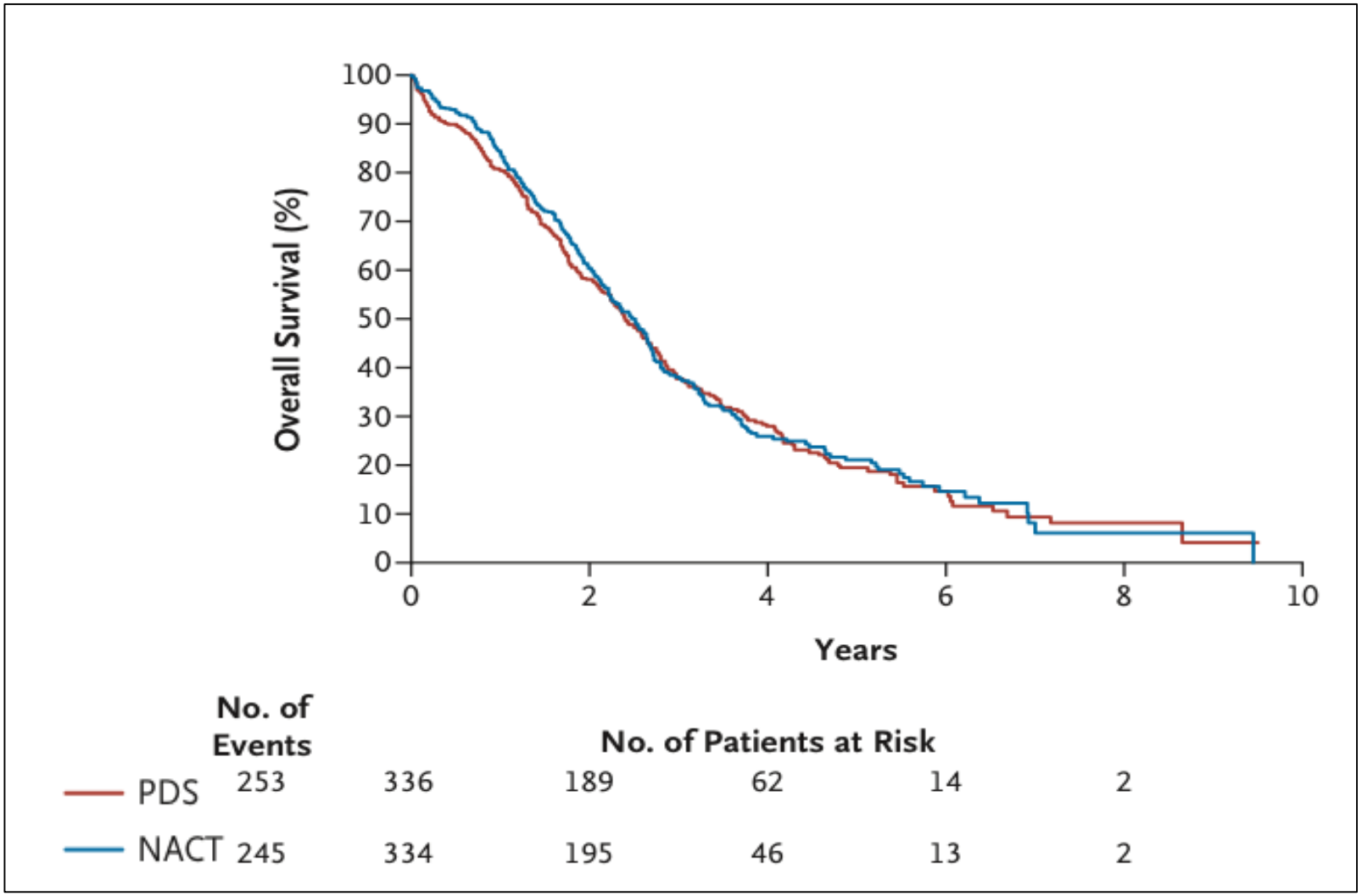
Ovarian, Tubal, or Peritoneal Cancer
FIGO Stage IIIC/IV (N = 670)



NACT = neoadjuvant chemotherapy; IDS = interval debulking surgery; PDS = primary debulking surgery; FIGO = International Federation of Gynaecology and Obstetrics; CT = chemotherapy; PD = progressive disease; QOL = quality of life; AEs = adverse events.
Vergote et al, 2008, 2010.

NACT + IDS Vs. PDS (cont.)

ITT Analysis



HR = hazard ratio.

Vergote et al, 2010.

First Line Treatment of Advanced Ovarian Cancer

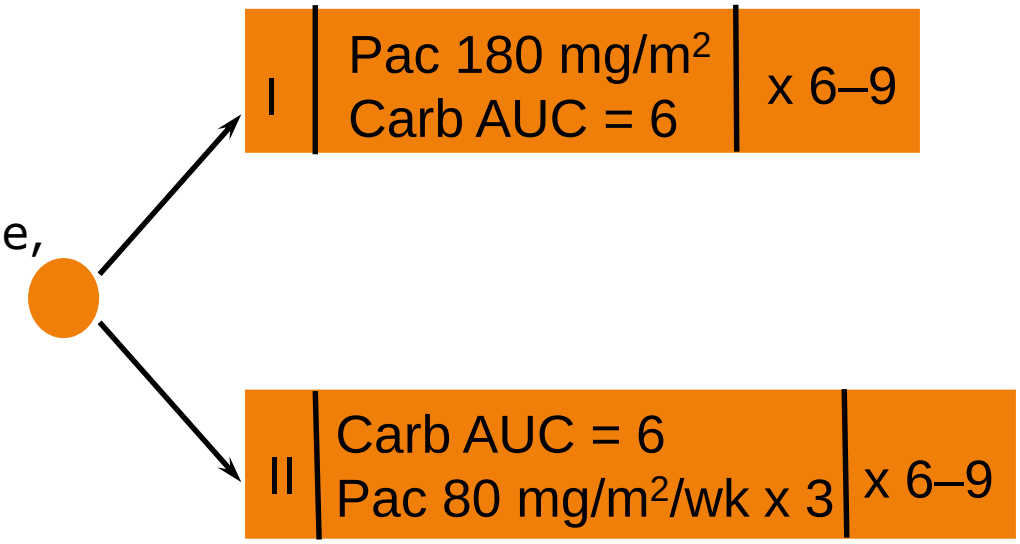
"Neoadjuvant" or Pre-Operative

OR

"Adjuvant" or Post-Operative

JGOG: Dose-Dense Wkly Paclitaxel

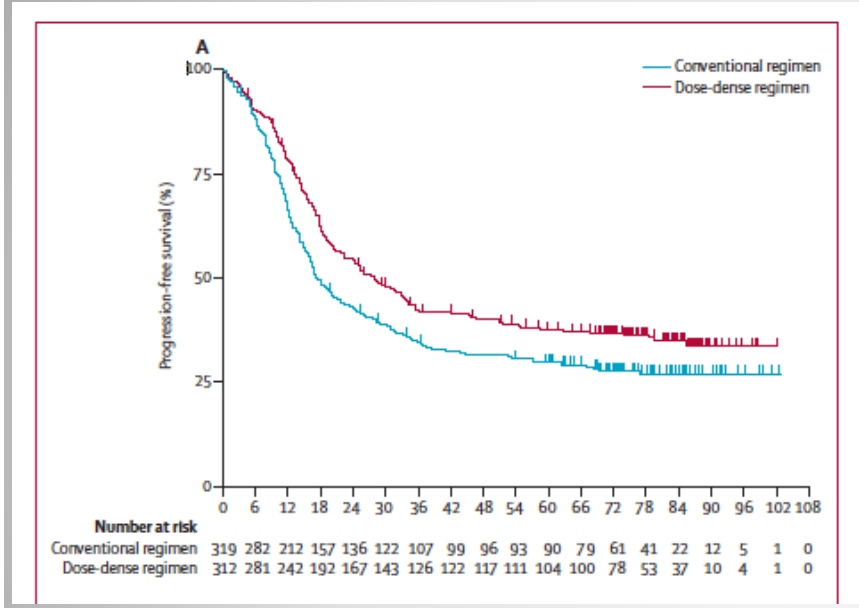
- EOC or PP
- Stage II–IV
- No prior therapy
- Stratified: Residual disease, stage, and histology
- Primary end point: PFS
- Secondary end point: OS

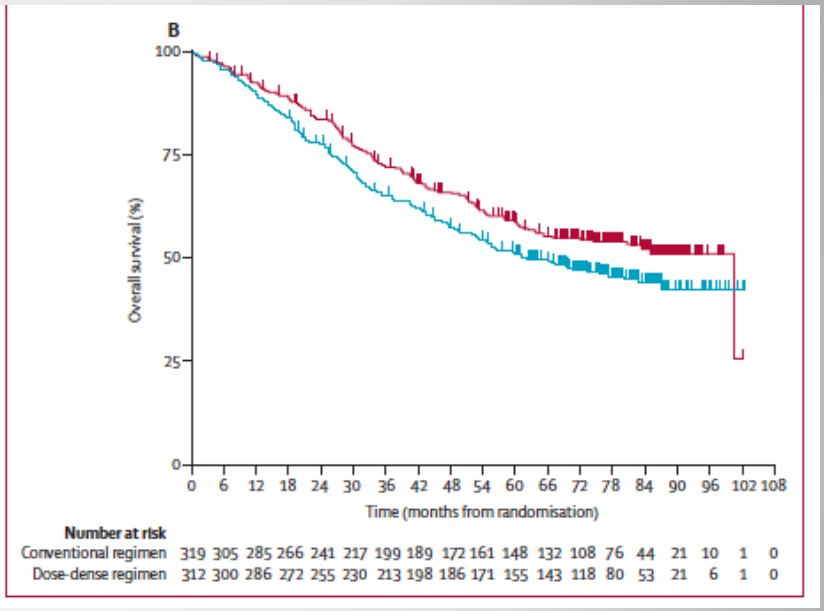


- ❖ Dose-dense paclitaxel associated with greater hematologic toxicity, and fewer patients completed all protocol therapy
- ❖ Improved PFS with dose-dense wkly paclitaxel

Accrual: 637 patients (ITT)

EOC = epithelial ovarian cancer; PP = primary peritoneal cancer; OS = overall survival; JGOG = Japanese Gynecologic Oncology Group; ITT = intent-to-treat; AUC = area under curve.
Isonishi et al, 2008.



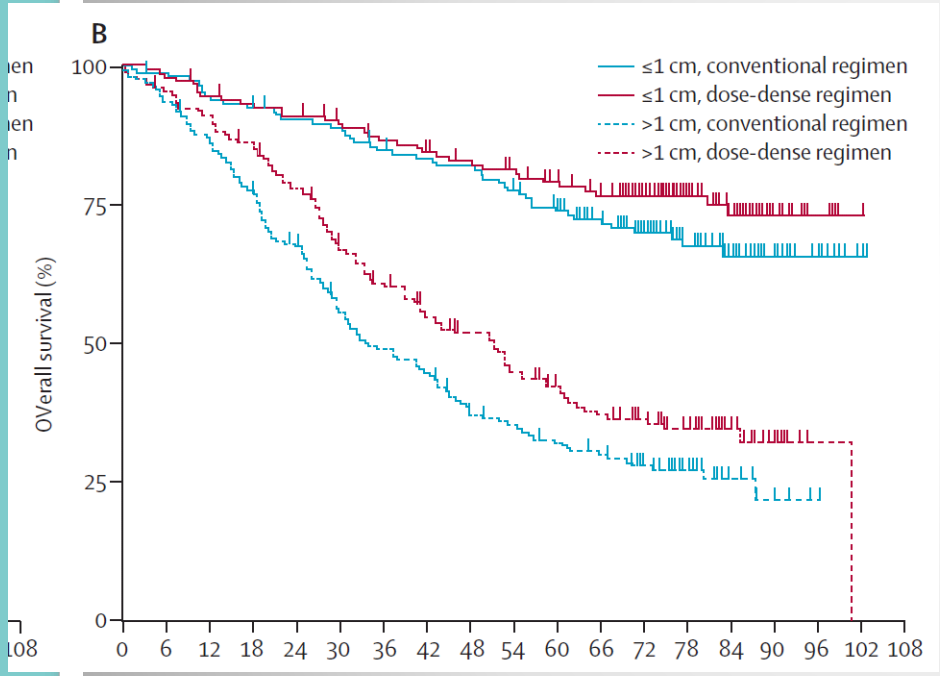


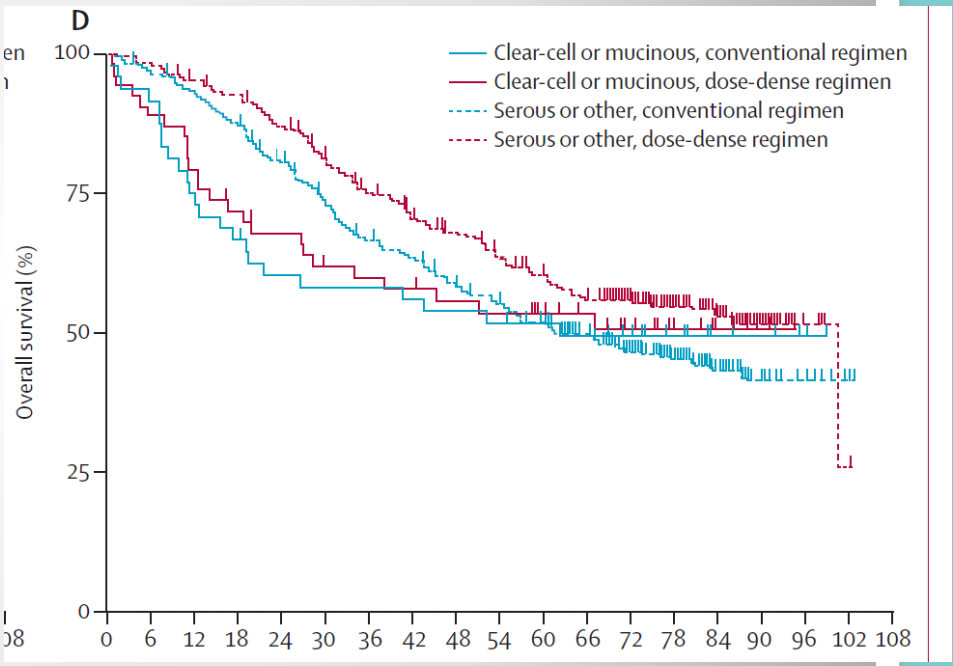
Treatment	n	Med OS	5-yr survival	*P* value	HR	95%CI
dd-TC	312	100.5	58.7%	0.039	0.79	0.63-0.99
c-TC	319	62.2	51.1%			

Katsumata, Lancet 2013

JGOG: Dose-Dense Wkly Paclitaxel

- By subgroups





Dose Dense Chemotherapy -JGOG

Katsumata et al Lancet Oncol 2013; 14: 1020–26.

- Dose-Dense Chemotherapy now standard in BC
  - Exclusions:
    - Clear cell and mucinous tumours
      - No known advantage (highly-resistant)
    - Cannot commit to weekly treatment
      - Social factors
      - Distance to travel
    - Medical reasons
      - High risk of neuropathy
      - Cannot tolerate dexamethasone
  - Alternative:
    - Historical standard:
      - 3 weekly therapy with carboplatin and paclitaxel
      - or another platinum based doublet

First Line Treatment: Pre-Operative

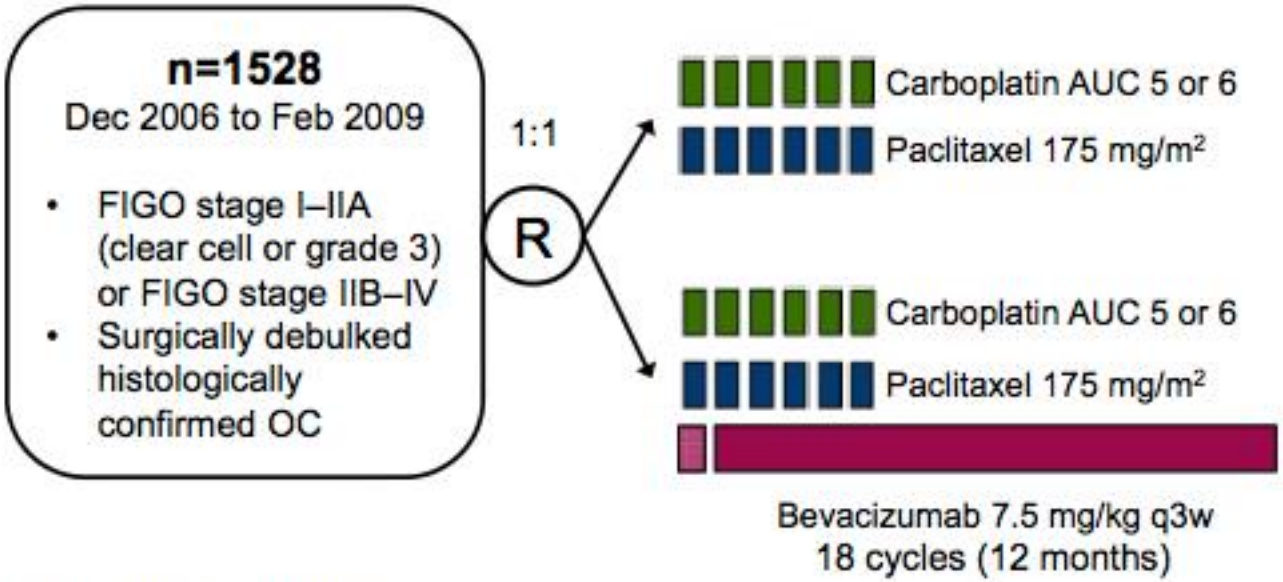
Role of Bevacizumab

- Bevacizumab has been approved by
  - Health Canada
  - pCODR
- First-line setting in “high-risk for recurrence” population
  - ICON-7

ICON7
Bevacizumab in Ovarian Cancer

Schema

MRC Clinical Trials Unit



Stratification variables:

- **Stage & extent of debulking** (I–III debulked ≤1cm vs I–III debulked >1 cm vs IV and inoperable stage III)
- **Timing of intended treatment start** (≤4 vs >4 weeks after surgery)
- **GCIG group**

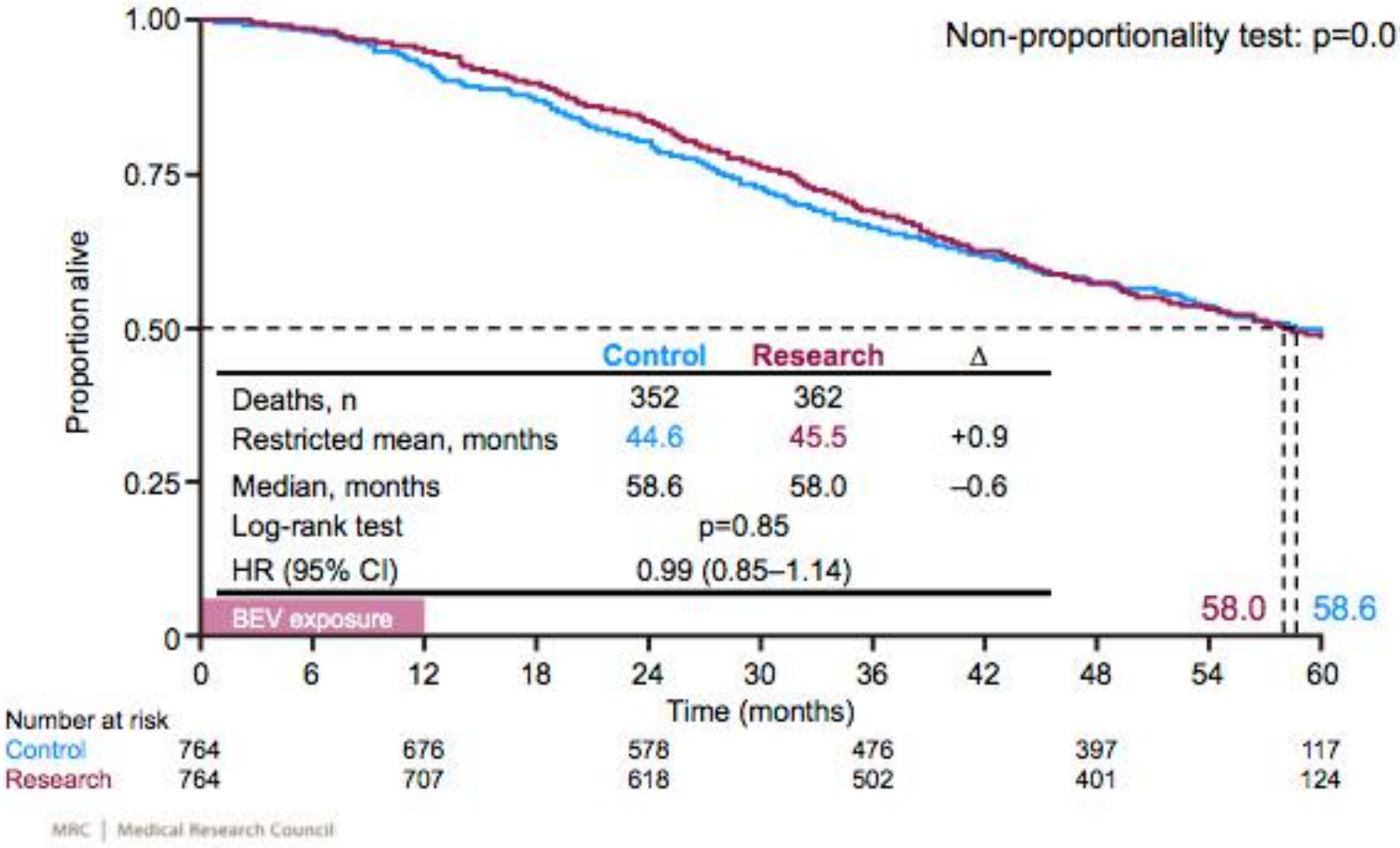
OC = epithelial ovarian, primary peritoneal or fallopian tube cancer

MRC | Medical Research Council

ICON7 Final OS (n=1528)

ICON7 Bevacizumab in Ovarian Cancer

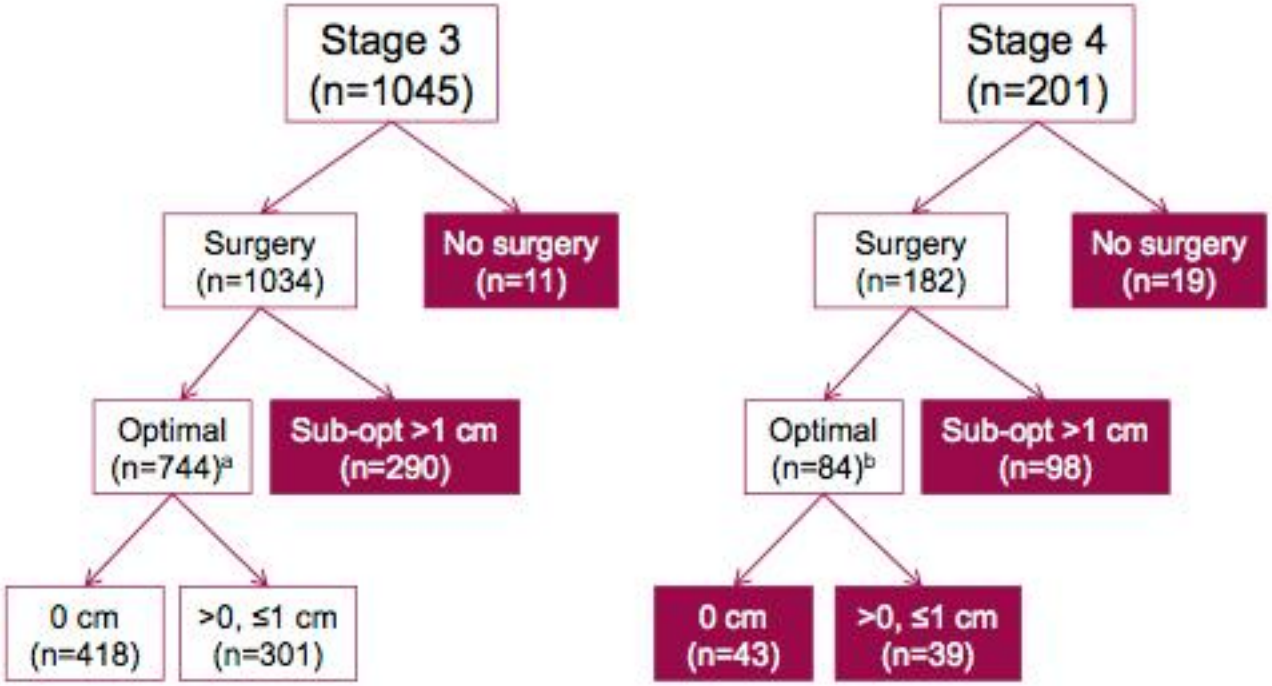
MRC Clinical Trials Unit



ICON7
Bevacizumab in Ovarian Cancer

Definition of high-risk subgroup

MRC Clinical Trials Unit



Modified ICON7 high-risk group (n=502)

Original ICON7 high-risk group (n=472)

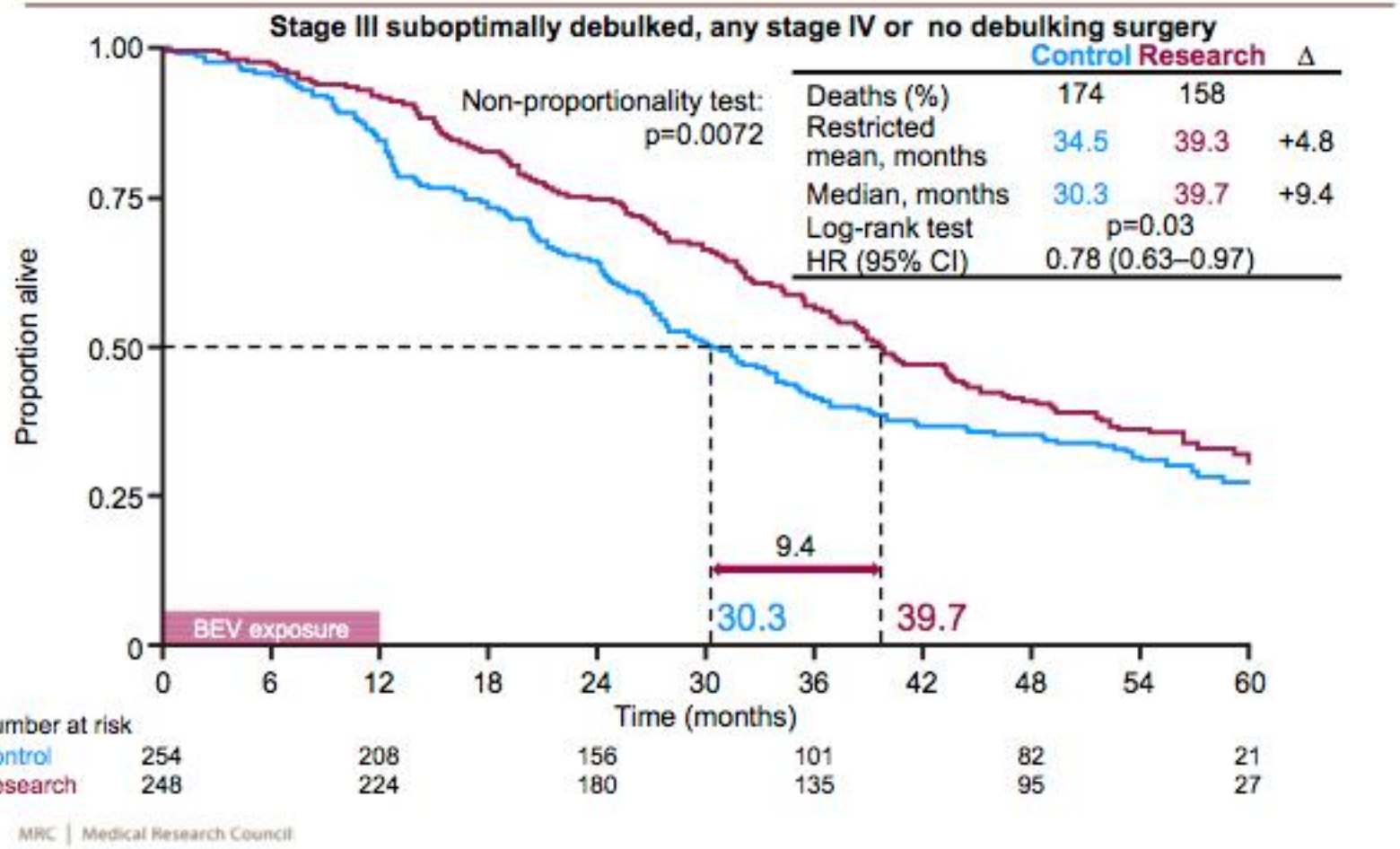
[a]Optimal unknown residual size (n=25)
[b]Optimal unknown residual size (n=2)

MRC | Medical Research Council

ICON7
Bevacizumab in Ovarian Cancer

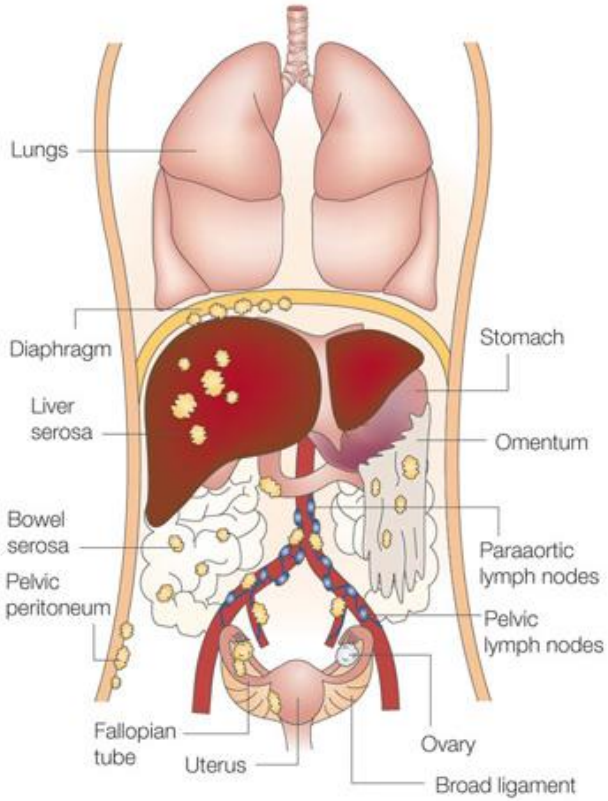
Final OS: High-risk (n=502)

MRC Clinical Trials Unit



Bevacizumab in First-Line Therapy

- Bevacizumab is available in some provinces in Canada:
  - First-line treatment
  - Upfront surgery
  - 3-weekly chemotherapy
  - For the "high-risk for recurrence" subgroup
    - Stage III with residual, or no surgery
    - Stage IV



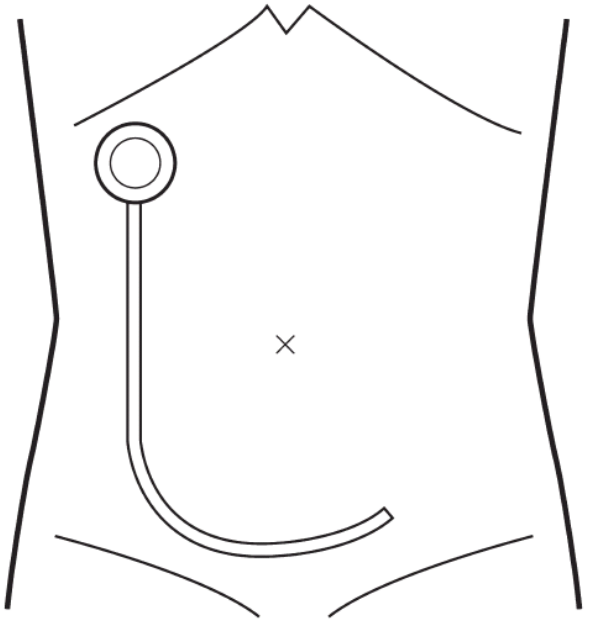


Figure 14. Preferred IP port system placement below the costal margin.

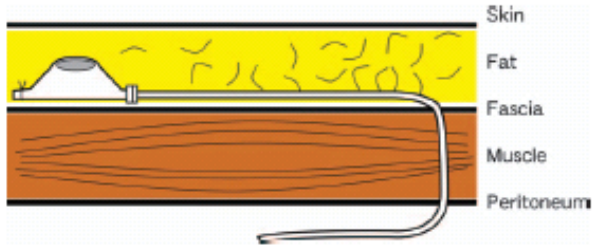


Figure 13. Preferred site for IP port system placement within the subcutaneous fat tissue above fascia.

Intraperitoneal Chemotherapy

- 3 trials
- IP therapy
- **stage 3, optimally debulked (< 1cm residual)**
- improvement in OS.

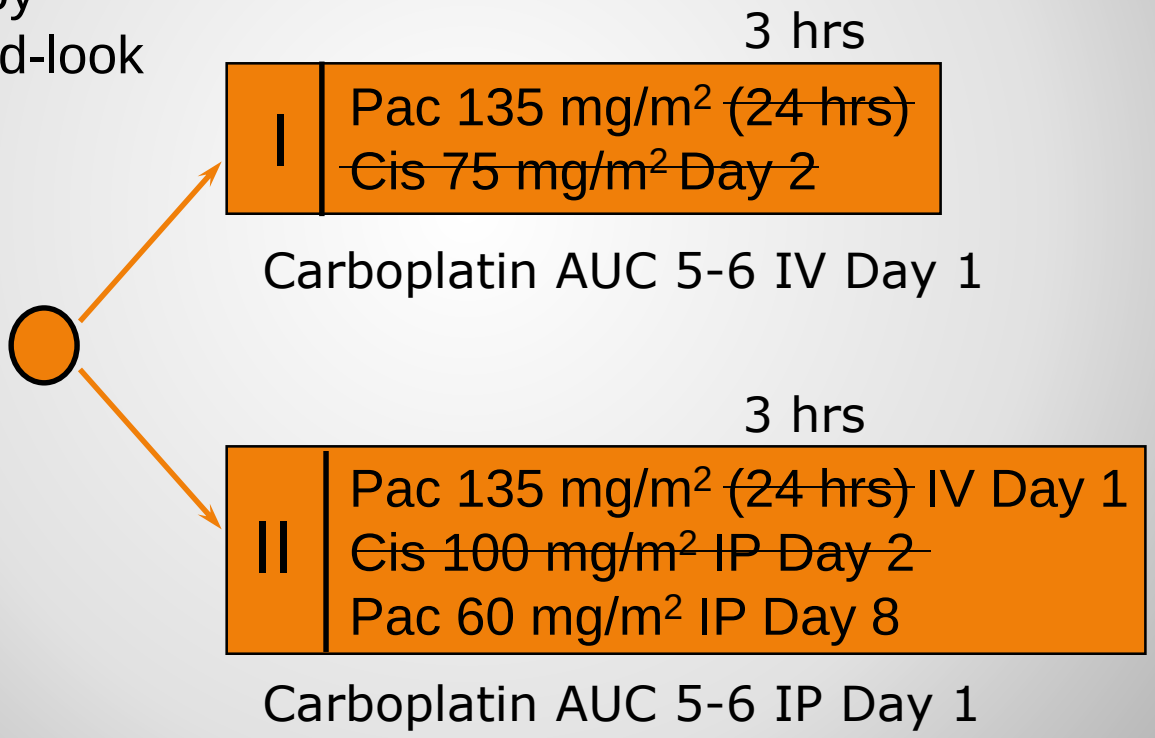
	Median PFS (mos)		HR	Median OS (mos)		HR
	IV	IP		IV	IP	
GOG 104	—	—	—	41	49	**0.76** (*p* = .02)
GOG 114	22	28	**0.78** (*p* = .01)	52	63	**0.81** (*p* = .05)
GOG 172	18.3	23.8	**0.80** (*p* = .05)	50	66	**0.75** (*p* = .03)

Primary Therapy: IP

Alberts et al, 1996; Markman et al, 2001; Armstrong et al, 2006.

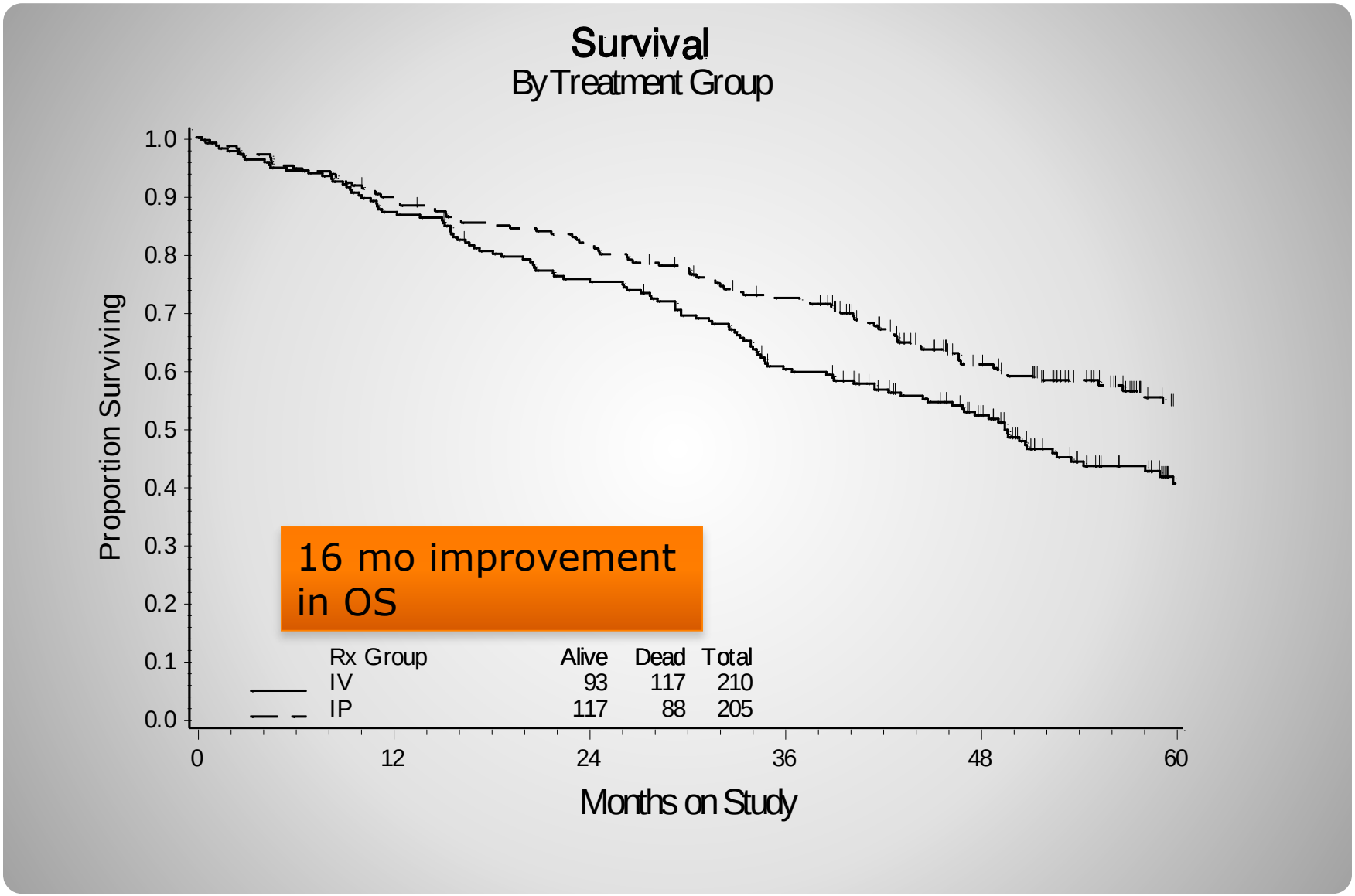
GOG 172: Ovarian (Optimal III)

- EOC
- Optimal stage III
- No prior therapy
- Elective second-look

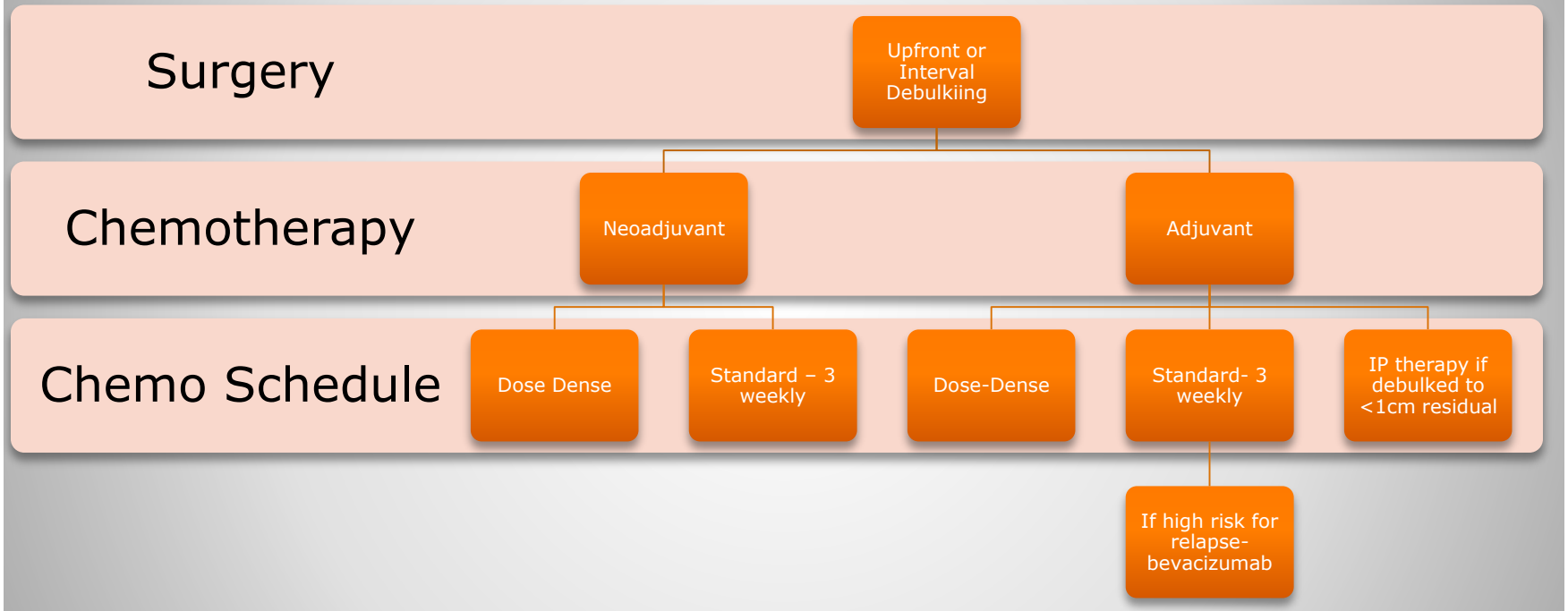


Accrual: 415 patients (evaluable)

Armstrong et al, 2006.



GOG-172 IP Chemotherapy



Summary of First-Line Therapy

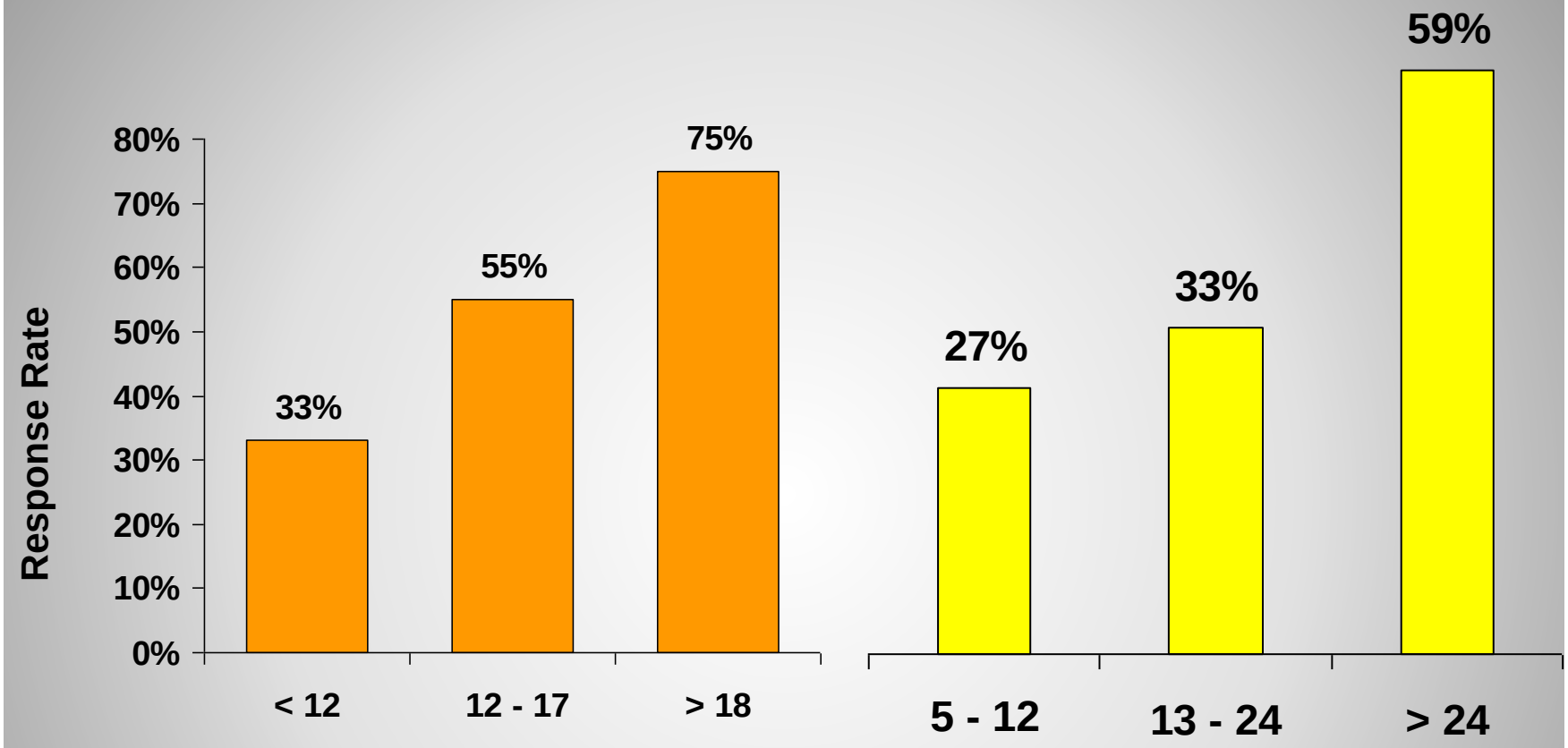
Treatment of Recurrent Ovarian Cancer

	Response to Platinum	
	Initial Response	Durable Response*
Platinum-sensitive	Yes	Yes
Platinum-resistant	Yes	No
Platinum-refractory	No	–

*Defined as disease recurrence > 6 months after initial platinum-based therapy

Duration of Response to First Line Therapy

Gadducci et al. *Anticancer Res*. 2001;21:3525-3533.



Effect of Platinum-Free Interval on Platinum Re-challenge

Markman et al. *J Clin Oncol*. 2004;22:3120-3125.

Markman et al. *J Clin Oncol*. 1991;9:389-93.

- Consider the platinum-sensitive interval
  - Assessed based on symptoms and imaging, and not on CA125 rise
    - after the use of initial therapy
      - not in 2nd, 3rd recurrence
      - most practitioners have expanded the definition beyond first-line

Recurrent Ovarian Cancer

Recurrence After First-Line Chemotherapy

Platinum Refractory/Resistant	Platinum Sensitive
< 6 Mos	> 6 Mos
Non-Platinum Single Agent	Chemotherapy Doublet

The Traditional Treatment Paradigm

Ushijima, 2010.

Recurrent Ovarian Cancer

- Platinum sensitive:
  - Return to platinum
    - as single agent
    - as a doublet
      - Carboplatin-paclitaxel
      - Carboplatin-liposomal doxorubicin
      - Carboplatin-gemcitabine
        - Choice is made by considering residual toxicity (neuropathy), comorbidities, convenience (travel)

Recurrent Ovarian Cancer

- Platinum resistant:
  - Consider sequential single agents
    - Carboplatin
    - Paclitaxel - +/- bevacizumab
    - Gemcitabine
    - Liposomal doxorubicinb+/- bevacizumab
    - Vinorelbine
    - Topotecan +/- bevacizumab
    - Etoposide

Role of Bevacizumab

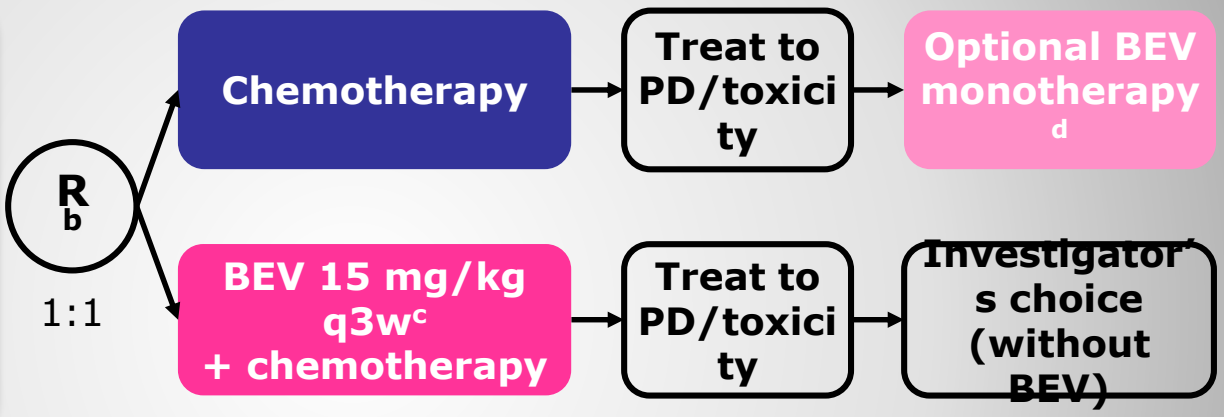
- Bevacizumab has been approved by
  - Health Canada
  - pCODR
- First-line setting in “high-risk for recurrence” population
  - ICON-7
- Platinum Resistant recurrence
  - AURELIA

AURELIA trial design

Platinum-resistant OC[a]

•≤2 prior anticancer regimens

•No history of bowel obstruction/abdominal fistula or clinical/ radiological evidence of rectosigmoid involvement



Primary endpoint: PFS (RECIST v1.0)

Secondary endpoints:

- ORR
- OS (after OS events in 70%)
- Quality of life
- Safety and tolerability

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

ORR = objective response rate; PD = progressive disease; PFS = progression-free survival;

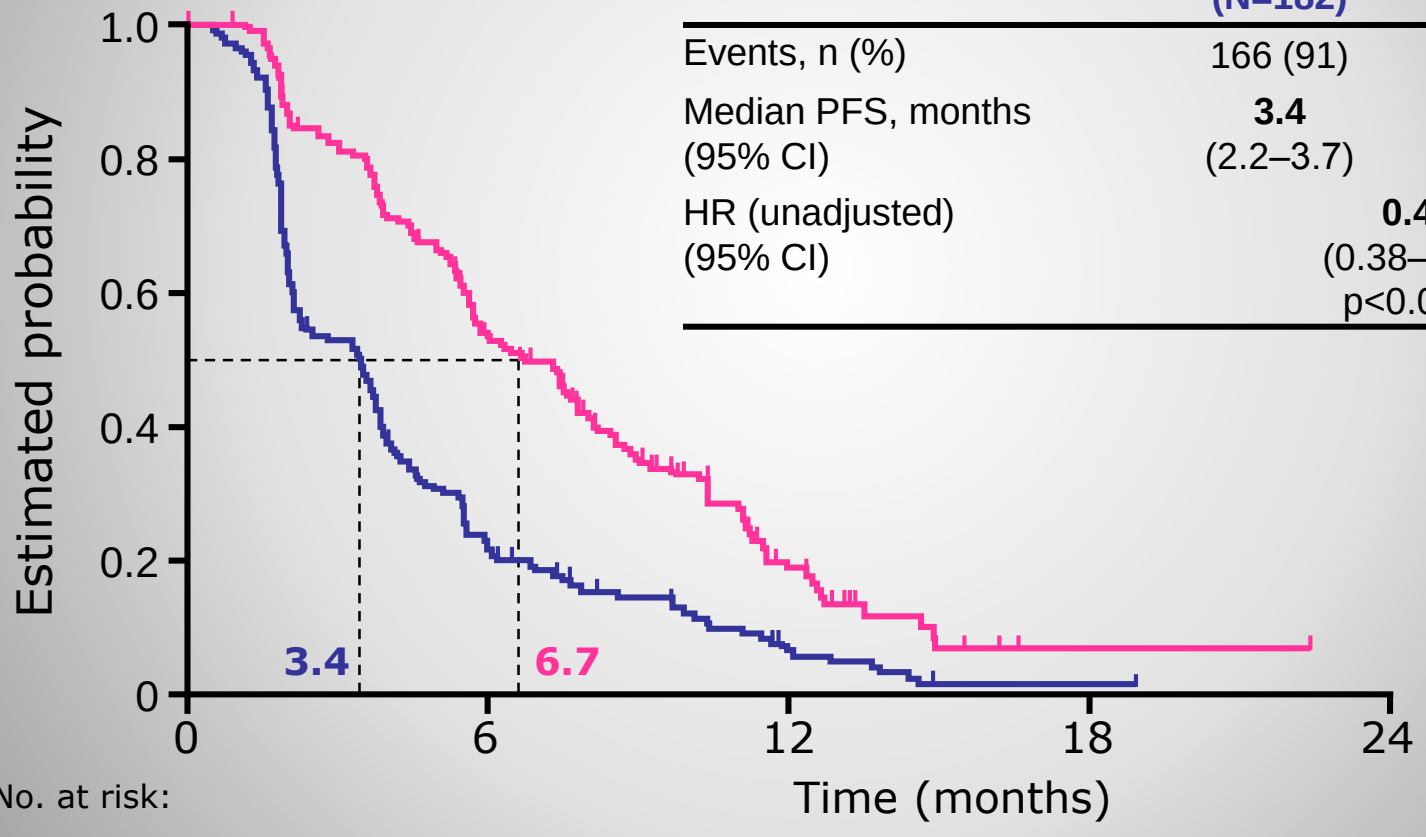
[a]Epithelial ovarian, primary peritoneal or fallopian tube cancer

[b]Stratification factors: selected chemotherapy; prior anti-angiogenic therapy; platinum-free interval (<3 vs 3–6 months)

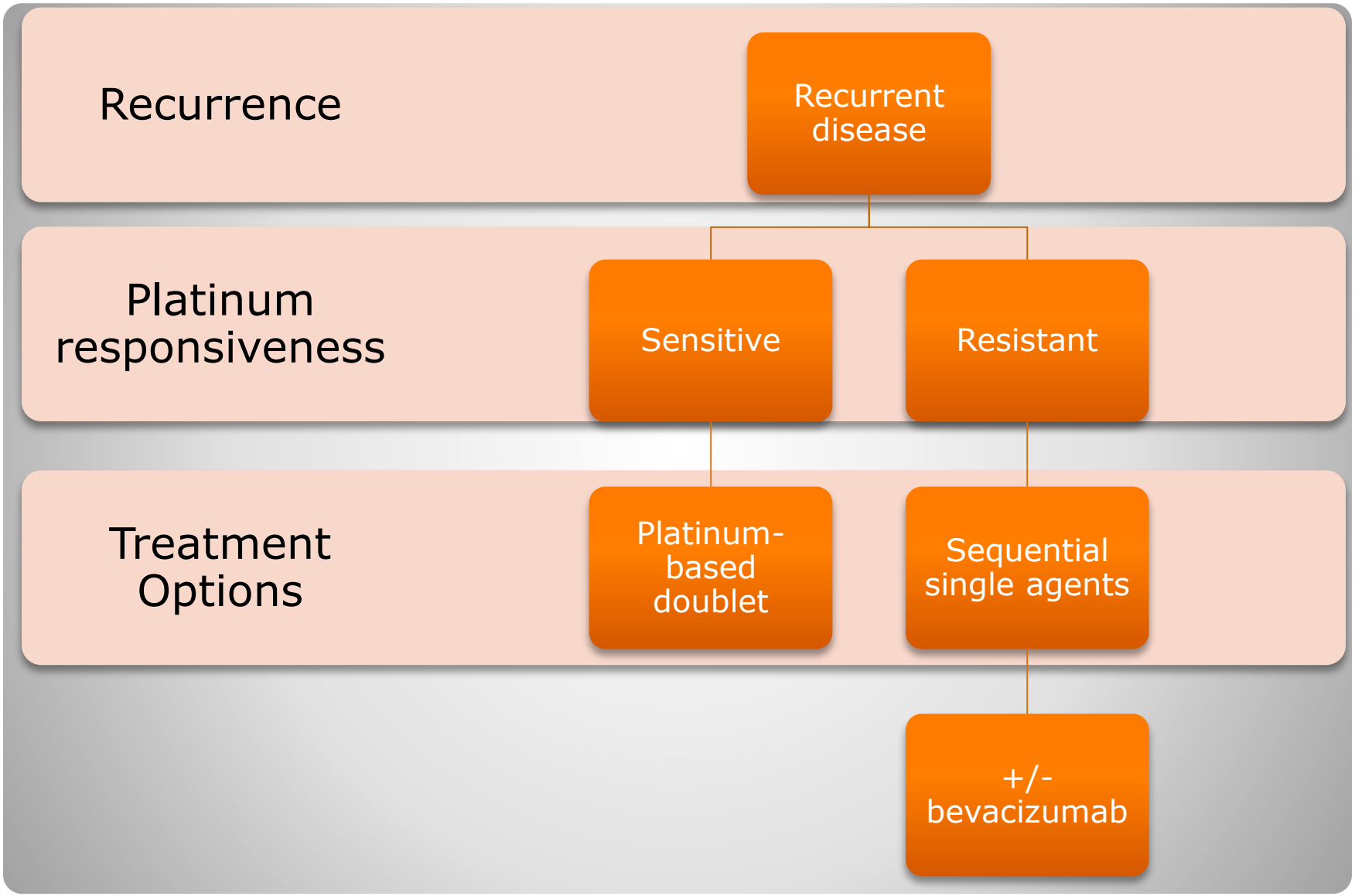
[c]Or 10 mg/kg q2w. [d]15 mg/kg q3w, permitted on clear evidence of PD

Primary PFS analysis

	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) p<0.001[a]	



Data cut-off: 14 November 2011. Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)
HR = hazard ratio
[a]2-sided log-rank, unadjusted



Treatment of Recurrent Disease

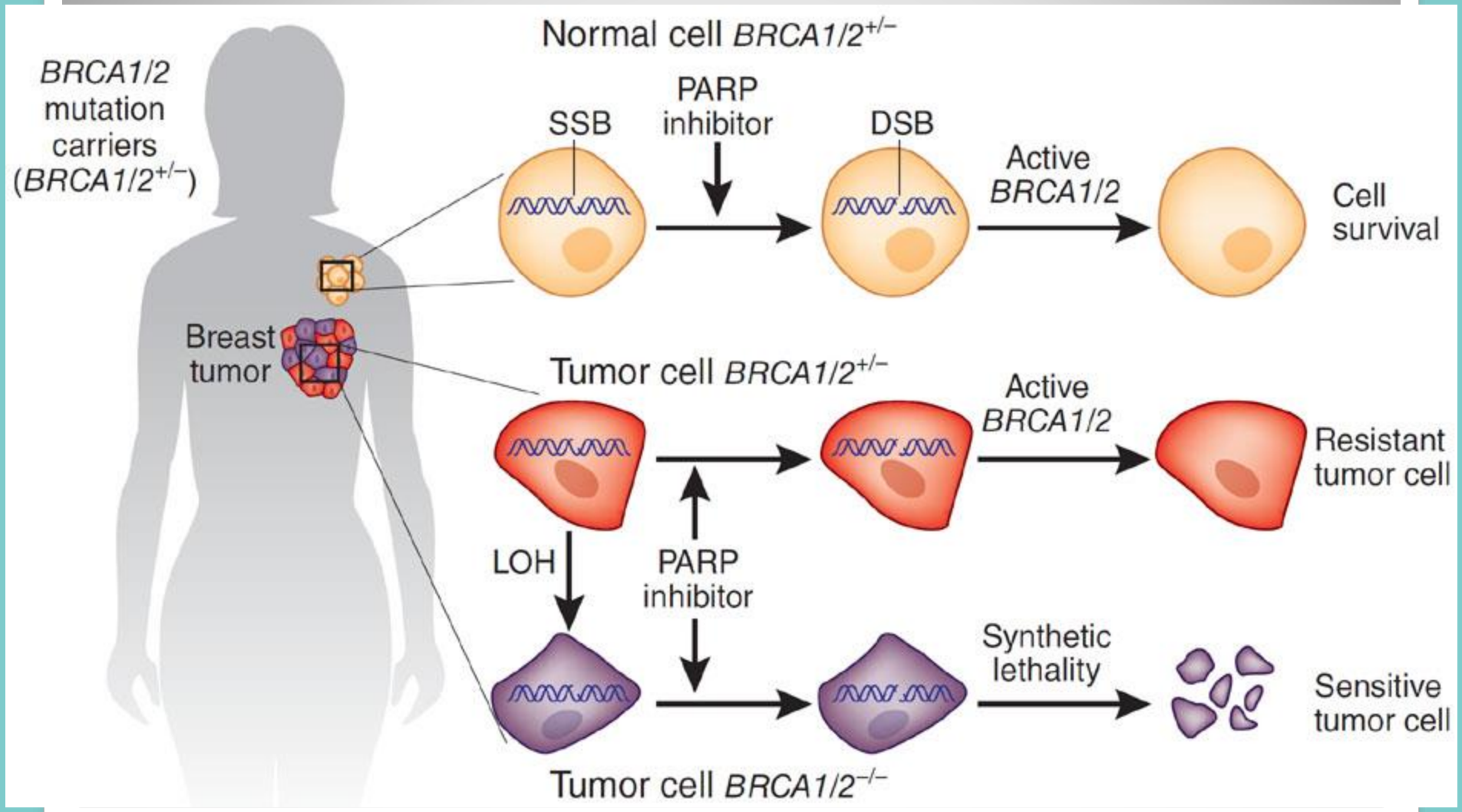
Parp Inhibitors

PARP Inhibitors

- PARP plays an important role in the repair of single-stranded DNA breaks
  - base excision repair pathway (BER) (high accuracy)
- Keep low-fidelity repair machinery in check
  - nonhomologous-end-joining DNA
  - Single strand annealing
- The other highly accurate DNA repair pathway is HR (double strand break repair)
- Many HGSC of the ovary have defects in the HR pathway
  - BRCA mutation
    - Germline = 25%
    - Somatic = 25%

PARP Inhibitors

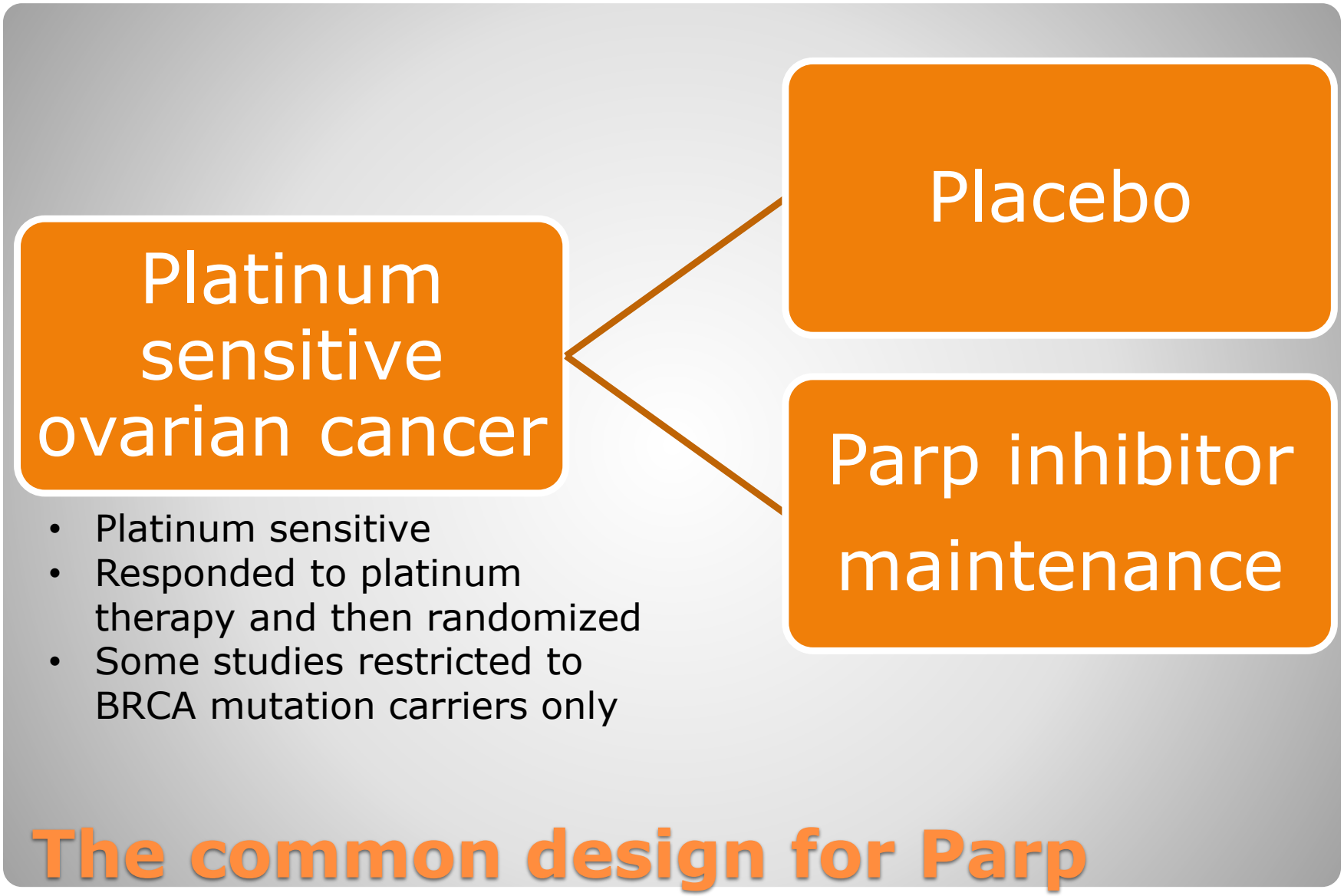
- When is LOH either by germline or somatic mutation in BRCA1/2, cell survival dependent on BER
- PARP inhibition leads to loss of BER
  - Mutation accumulation
  - “mitotic catastrophe”
  - Apoptosis
  - Normal cells have preserved HR function and are not susceptible to the PARP inhibitor
- Synthetic Lethality
  - whereby two conditions independently would not cause cell death, but in combination are lethal



Synthetic Lethality

PARP Inhibitors

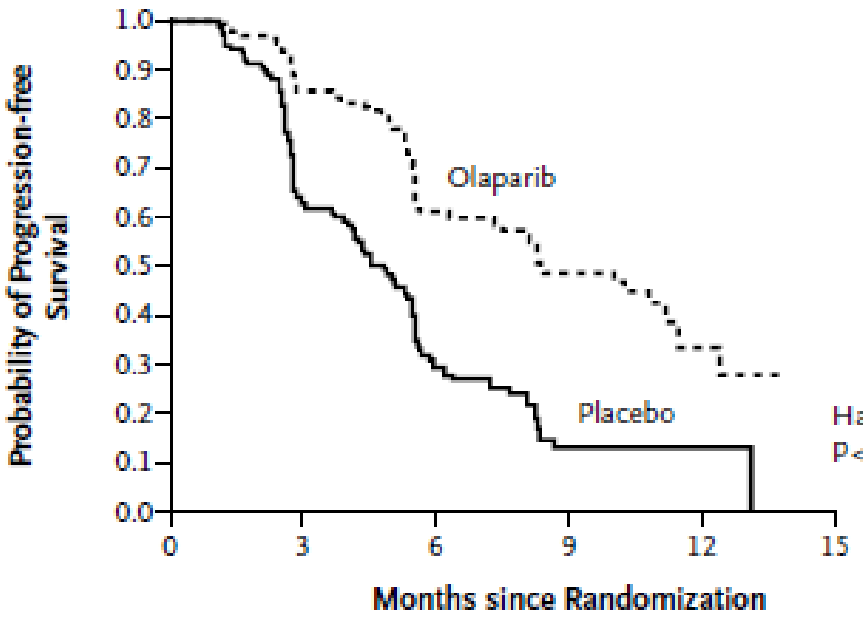
- Used as single agents as do not combine well with chemotherapy
  - Myelosuppression
- Oral drugs
- Generally well tolerated
  - Fatigue, anorexia, nausea, anemia, thrombocytopenia, neutropenia, elevation of LFTs, rise in Cr
  - No hair loss
  - No neuropathy
  - Most patients state that better than chemo in terms of side effects



- Platinum sensitive
- Responded to platinum therapy and then randomized
- Some studies restricted to BRCA mutation carriers only

The common design for Parp inhibitor trials

A



Hazard ratio, 0.35 (95% CI, 0.25–0.49)
P<0.001

No. at Risk							No. of Patients/ Total No. (%)	Median Progression-free Survival (mo)
Olaparib	136	104	51	23	6	0	60/136 (44.1)	8.4
Placebo	129	72	23	7	1	0	93/129 (72.1)	4.8

Randomized Phase II of Maintenance PARPi in Plt Sensitive Recurrent OvCa

TESARO

September 12, 2016

TESARO Receives FDA Fast Track Designation for Niraparib and Initiates Rolling NDA Submission

TESARO'S NIRAPARIB SIGNIFICANTLY IMPROVED PROGRESSION-FREE SURVIVAL FOR PATIENTS WITH OVARIAN CANCER IN BOTH COHORTS OF THE PHASE 3 NOVA TRIAL

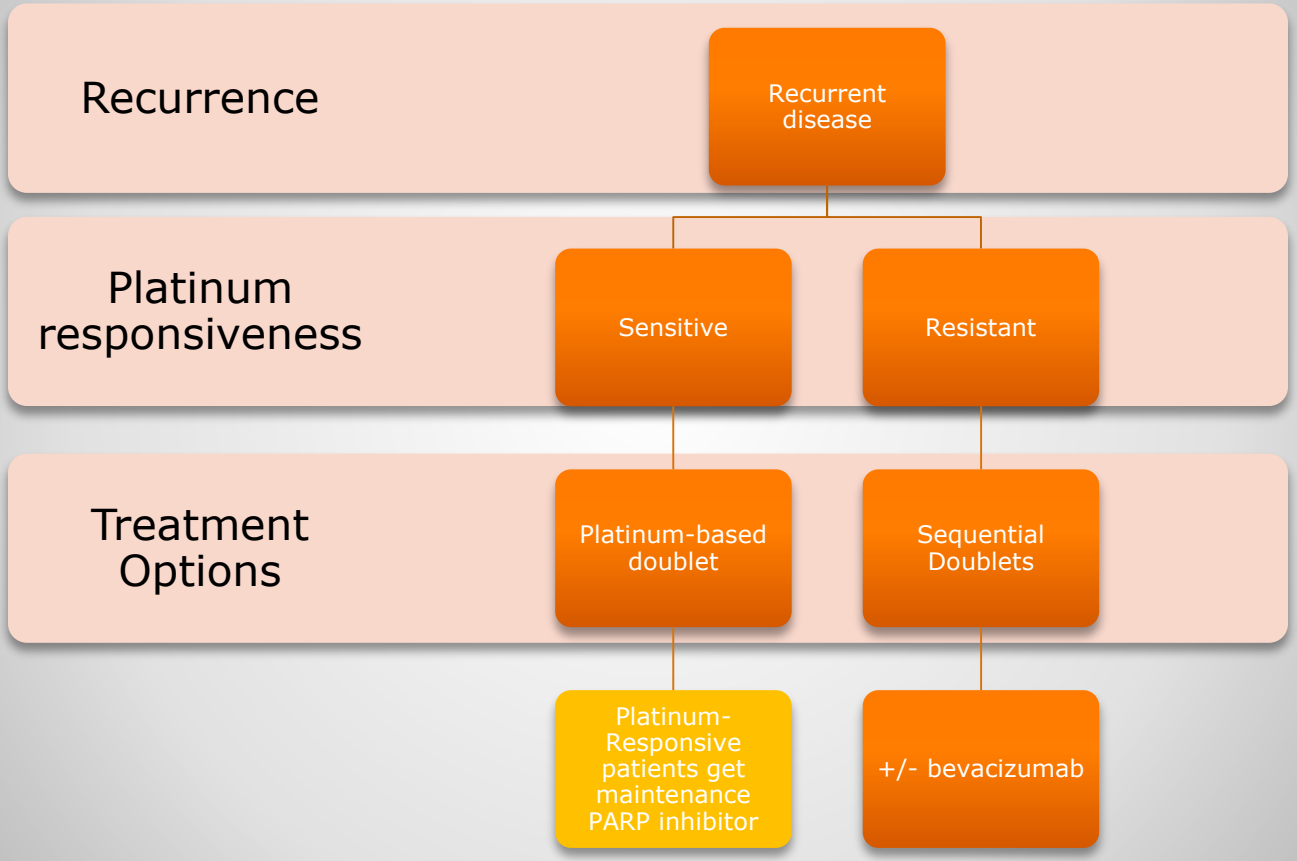
- The NOVA trial successfully achieved its primary endpoint of PFS in the germline BRCA mutant cohort
- The NOVA trial successfully achieved its primary endpoint of PFS in the non-germline BRCA mutant cohort, including both the HRD-positive and overall analysis populations
- NOVA is the first successful prospectively designed Phase 3 trial of a PARP inhibitor
- NDA and MAA submissions are planned for Q4 2016

Other Parp Inhibitors

Other Parp Inhibitors

PARP inhibitors in Canada

- Health Canada has approved the sale of olaparib in Canada
- pCODR has reviewed the evidence and did not recommend public reimbursement



Treatment of Recurrent Disease – the possible future

PARP inhibitors

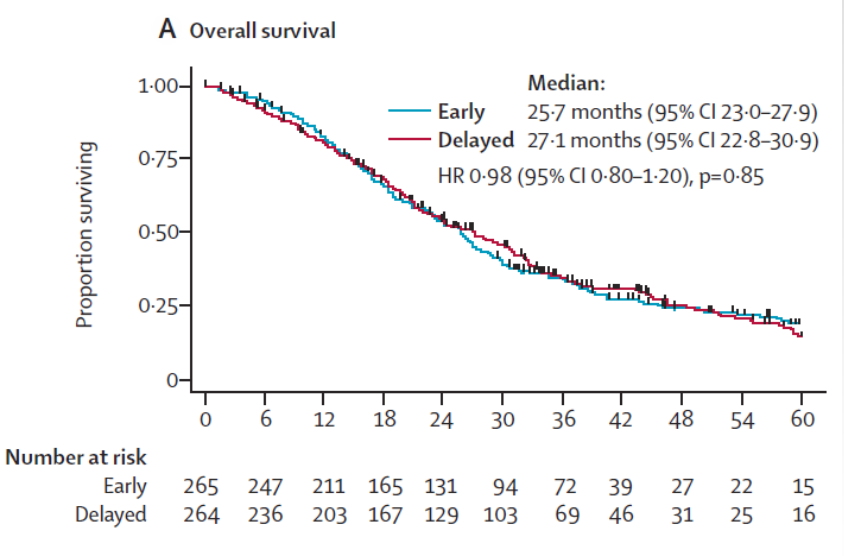
- Phase 3 trials are ongoing
  - Maintenance in the first-line setting also being tested
  - BRCA mutation carries
  - HGSCs and a companion predictive test for PARP benefit

- How often should patients be followed?
- What is the value of the CA-125 in detecting recurrence?
- What is the benefit of early treatment initiation?

Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial

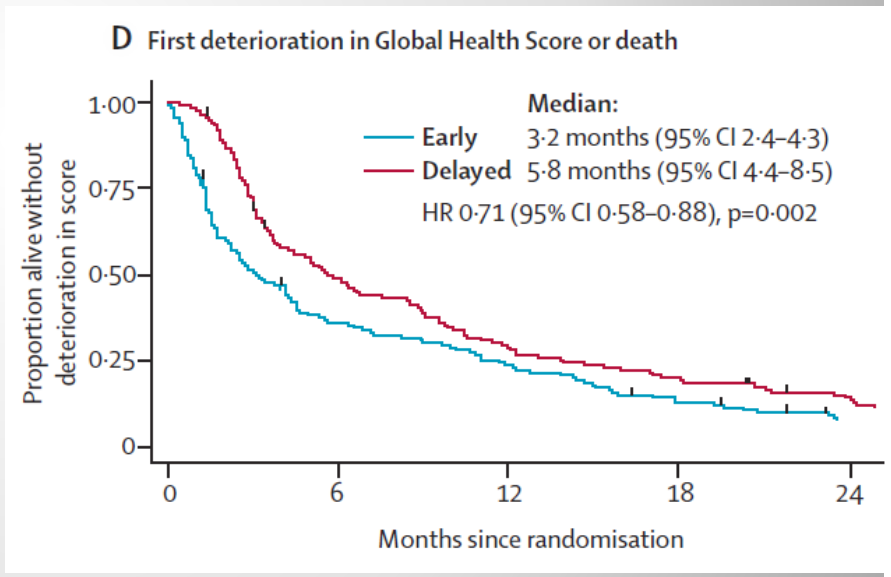
*Gordon J S Rustin, Maria E L van der Burg, Clare L Griffin, David Guthrie, Alan Lamont, Gordon C Jayson, Gunnar Kristensen, César Mediola, Corneel Coens, Wendi Qian, Mahesh K B Parmar, Ann Marie Swart, for the MRC OV05 and EORTC 55955 investigators**

Follow-up post first-line therapy



Early treatment group:

- Early deterioration in QoL
  - Emotional, social, fatigue



Early treatment group:

- average started chemo 4.8 mo earlier
- Received more 2nd line chemo (6 cycles 64% vs 51%)
- Received more 3rd line chemo(67% vs 54%)

Early Vs Delayed Chemo at Relapse

Post treatment follow up

- The best evidence suggests that monitoring of CA-125
  - Does not improve outcomes
  - Leads to premature deterioration in QoL
- There are no evidence based guidelines for post treatment monitoring
  - Discourage routine CA125
  - Encourage standard “Clinical” follow up – ROS and examination

Summary

- Ovarian cancer is not ovarian
  - …fallopian and endometrial origins explain most
- Surgery timing can be up front or delayed
- IP chemotherapy has the best up front survival data so far
- Drug schedules matter
  - Dose-dense treatment appears to be better
  - Addition of bevacizumab may prolong OS

Summary

- Platinum Sensitive disease
  - Platinum doublets, or single agent
  - Maintenance with Parp-inhibitors may become standard for platinum sensitive recurrences
- Platinum resistant disease
  - Poor prognosis, use single agents +/- bevacizumab
- Follow up
  - Clinical only – no benefit to early treatment at relapse

Thank you for listening!