INTERNATIONAL GYNECOLOGIC CANCER SOCIETY

MADRID 2014 ESMO congress

Targeted Therapy in Gynecologic Cancer: *The Coming Decade*

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NRG ONCOLOGY
Advancing Research. Improving Lives.™

GOG Gynecologic Oncology Group

THE UNIVERSITY OF ARIZONA CANCER CENTER

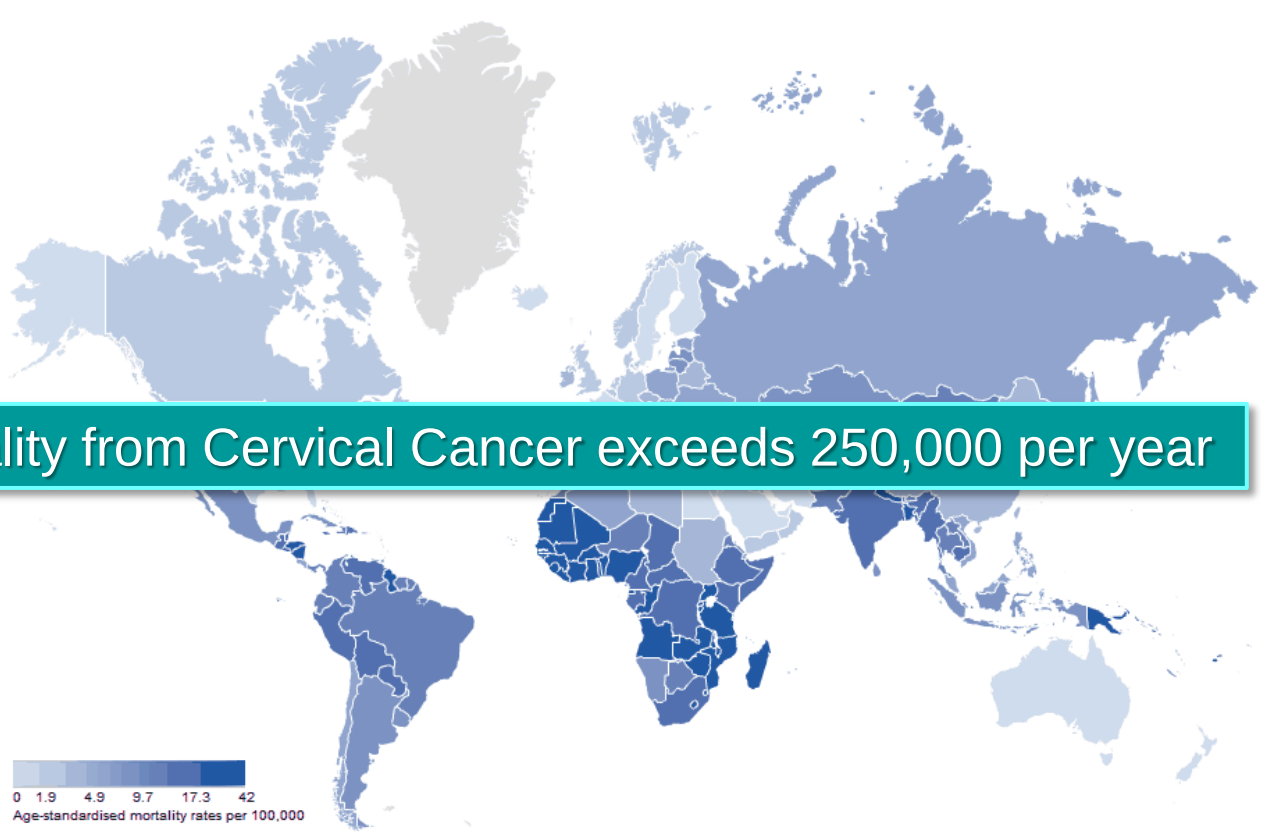
Welcome to Cordoba!

Relevant Disclosures

- Member of Independent Data Safety Monitoring Boards (DSMB) for phase III trials, Genentech-Roche and Boehringer-Ingelheim (compensated for effort)
- Participant in ad-hoc advisory boards for pharmaceutical industry regarding design of trials using investigational agents (travel support and honoraria).
- No financial holdings in pharmaceutical industry
- No marketing relationships
- Chair, Ovarian Committee, NRG-GOG
- Predictions are “forward looking statements” without any guarantees or warranties. Actual performance over the next decade may vary…

Cervical Cancer: Global Mortality

Not all high-priority targets are molecular!



Global Mortality from Cervical Cancer exceeds 250,000 per year

Ferlay J, et al. GLOBOCAN 2008 v2.0: International Agency for Research on Cancer

http://globocan.iarc.fr

Targeting Cervical Cancer

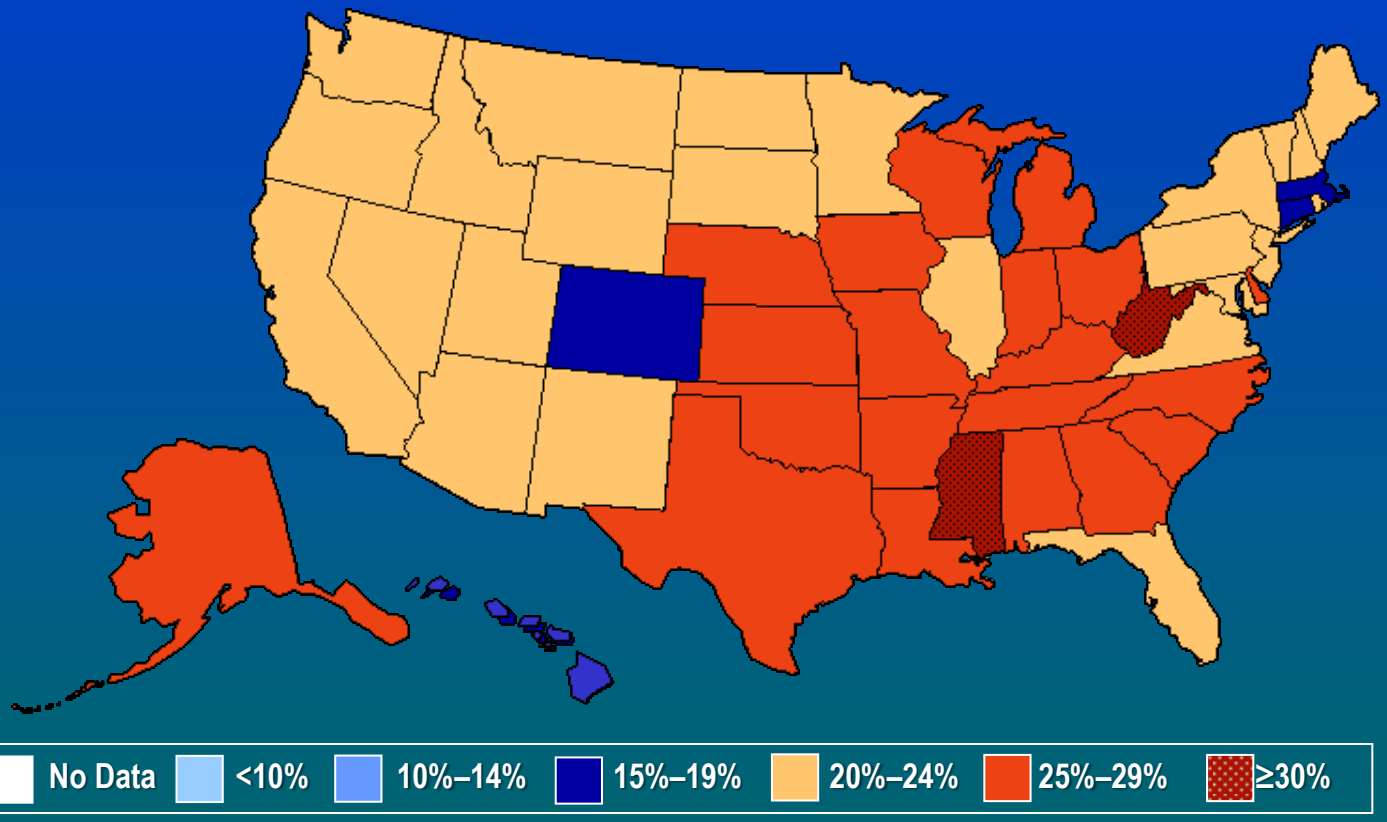
	Risk Factors	Intervention
Etiology	HPV Exposure	• Vaccine (pre-exposure)
Additional Risks	HPV Chronic Infection	• Smoking (Immune Suppression) • Cervical Trauma and Inflammation (Basal Access)
Screening	Socioeconomic Status, Politics, and Culture	• HPV and/or Cytology (min x1)
Prevention		• Ablation of pre-invasive disease
Primary Therapy (regional)	Inadequate Screening	• Surgery and/or Chemoradiation +/- Adjuvant Chemotherapy
Primary Therapy (advanced/recurrent)	Platinum Resistance Tumor Angiogenesis Tumor Hypoxia	• Prevention (as above) • Tailored Radiation, Surgery, and Chemotherapy • Incorporation of Bevacizumab and Investigational Agents

Targeting Cervical Cancer

- HPV Vaccination and Screening
  - Strategies tailored for the developing world, and immigrant populations within the developed world
  - Collaboration among public health agencies, NGOs, and foundations (not always easy)
  - Focus on younger generation, social media, information resources
  - Attention to other risk-altering modifications (*i.e.*, smoking)
  - Greatest reduction in mortality from ONE screening cycle
- Therapy
  - Emphasis on early interventions for non-invasive disease and monitoring for residual HPV infection
  - Availability of radiation facilities in low-resource settings
  - Targeting angiogenesis and hypoxia in high-resource settings
  - Pharmacologic inhibition of HPV-E6 function (or MDM2/4) to restore P53 function

Obesity Trends, US Adults (BMI ≥30)

1985 1990 1995 2000 2005 2006



Source: CDC Behavioral Risk Factor Surveillance System.

Targeting Endometrial Cancer

	Type I	Type II
Median Age	50 - 60	60 - 70
Estrogen Related	Common	Uncommon
Obesity	Common	Uncommon
Background	Hyperplasia	Atrophic
Precursor	EIN	EGD, EIC
Histology	Endometrioid	Serous, Clear Cell
Molecular Alterations	MLH/MSI, PTEN, K-RAS, FGFR2, β-Catenin	p53, 17p del, HER2/neu
Detection	Early-Stage	Advanced-Stage
Familial Risk	HNPCC	BRCA (serous)
Spread	LN, Distal	LN, Peritoneal

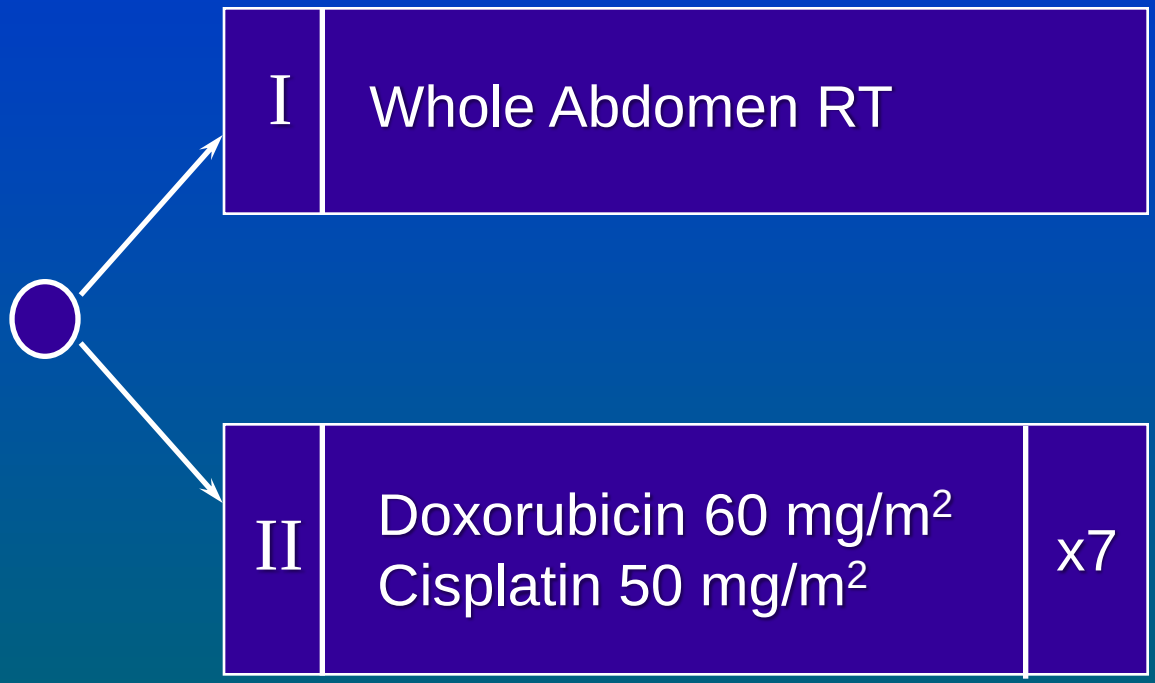
Targeting Endometrial Cancers (I & II)

Gene	Abnormality	Prevalence of Abnormality	
		Type I	Type II
PIK3CA	Amp	2-14%	46%
PIK3CA	Mut	26-36%	26-36%
KRAS	Mut	13-26%	0-10%
TP53	Mut	5-10%	80-90%
MLH1	Meth/Mut	20-35%	0-10%
MSI	Meth/Mut	20-45%	0-5%
ER, PR	Exp	70-73%	19-24%
HER2/ERBB2	Amp/Exp	Rare	18-80%
PTEN	Mut/Del/Meth	35-55%	0-11%
Stathmin	Exp	15%	64%
CDKN2A	Mut/Meth/Exp	10%	10-40%
β-Catenin	Mut	25-38%	0-5%

Modified from: Salvesen HB, et al. *Lancet Oncol* 2012; 13: e353–61

GOG122: WART *vs* Chemotherapy

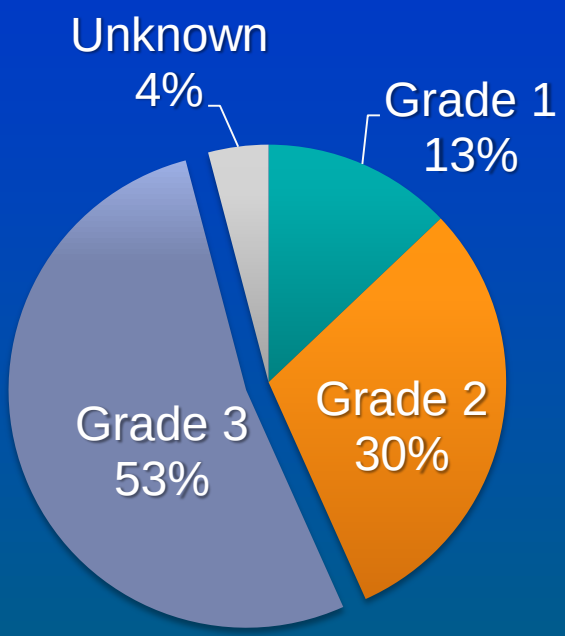
- Adenocarcinoma
- Stage III/IV
- No prior chemotherapy
- PA LN (+/-) Scalene (-)
- Reductions for prior RT

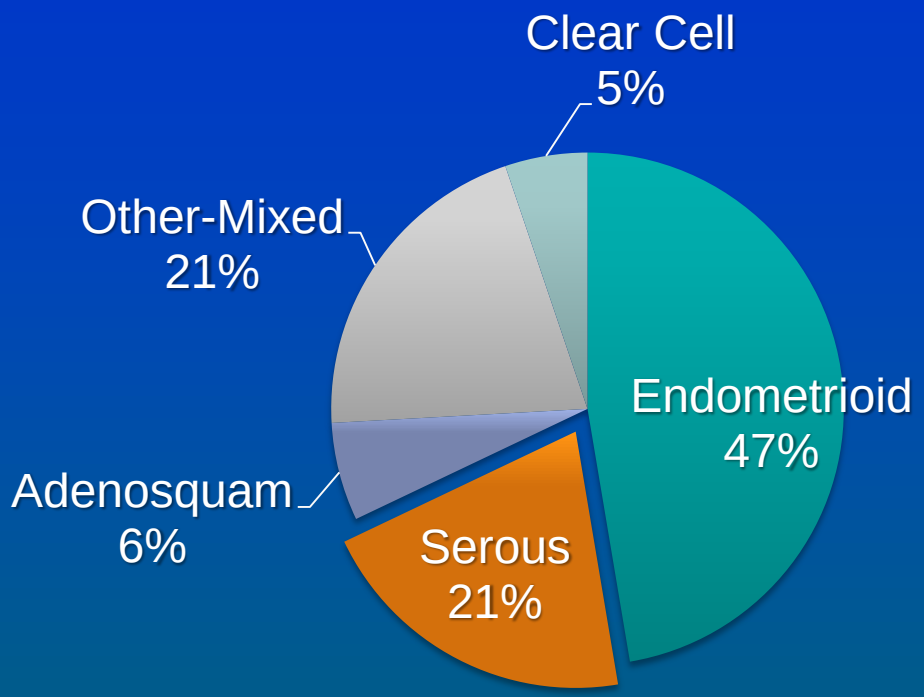


Open: 04-May-92
Closed: 25-Feb-00
Accrual: 388 pts

Randall, et al. *J Clin Oncol* 24:36-44, 2006

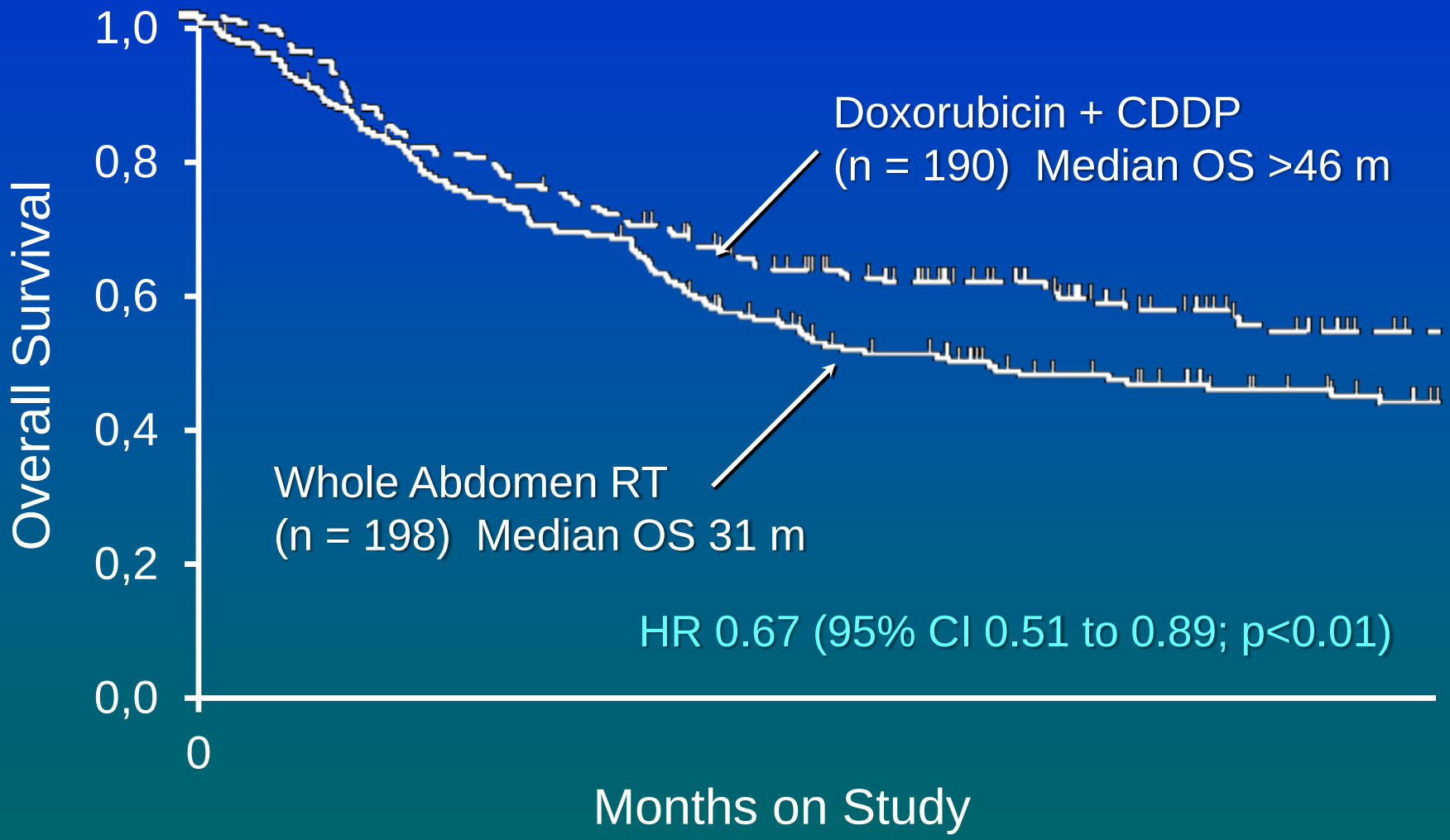
GOG122: Tumor Characteristics





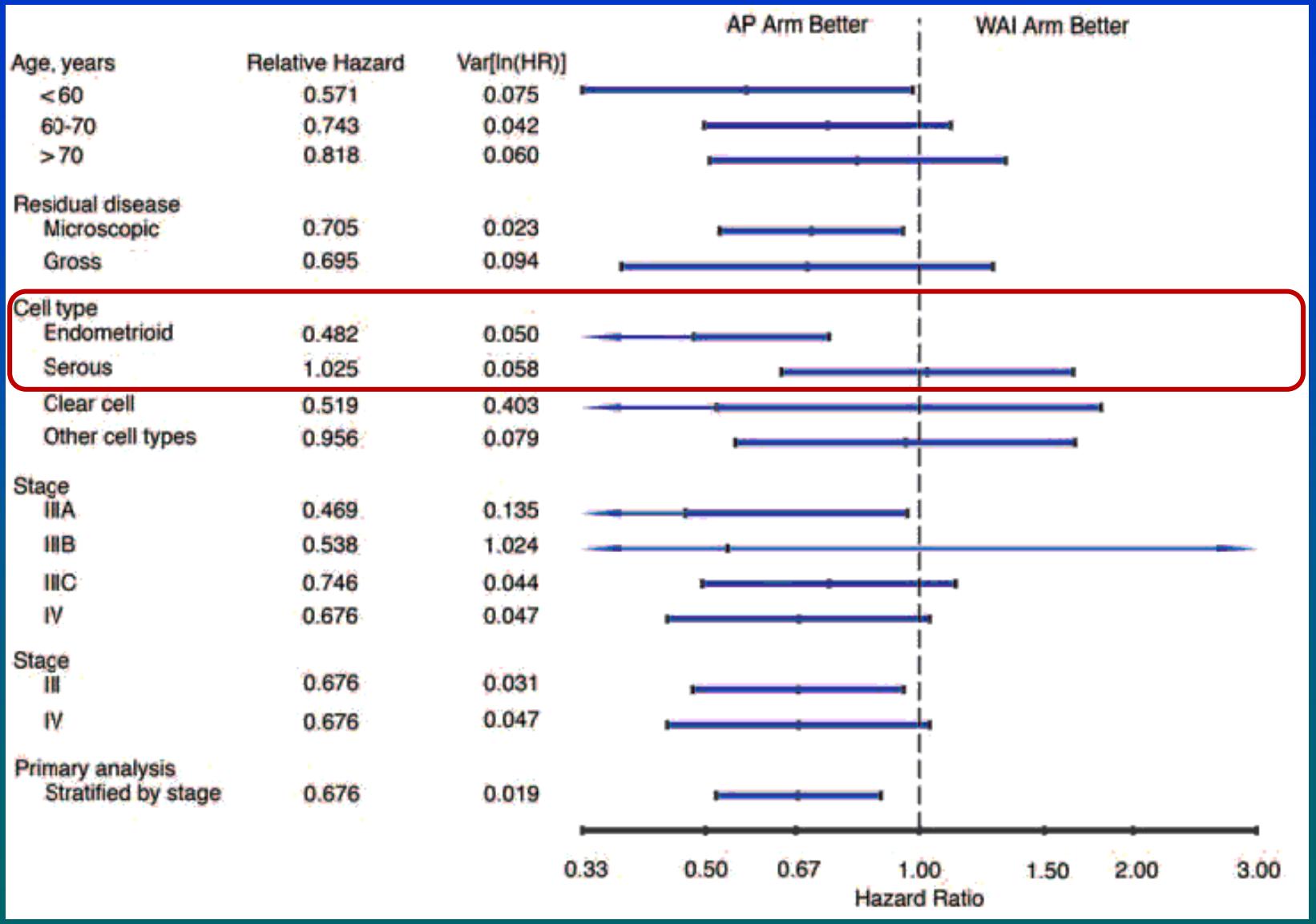
Randall, et al. *J Clin Oncol* 24:36-44, 2006

GOG122: Overall Survival by Treatment



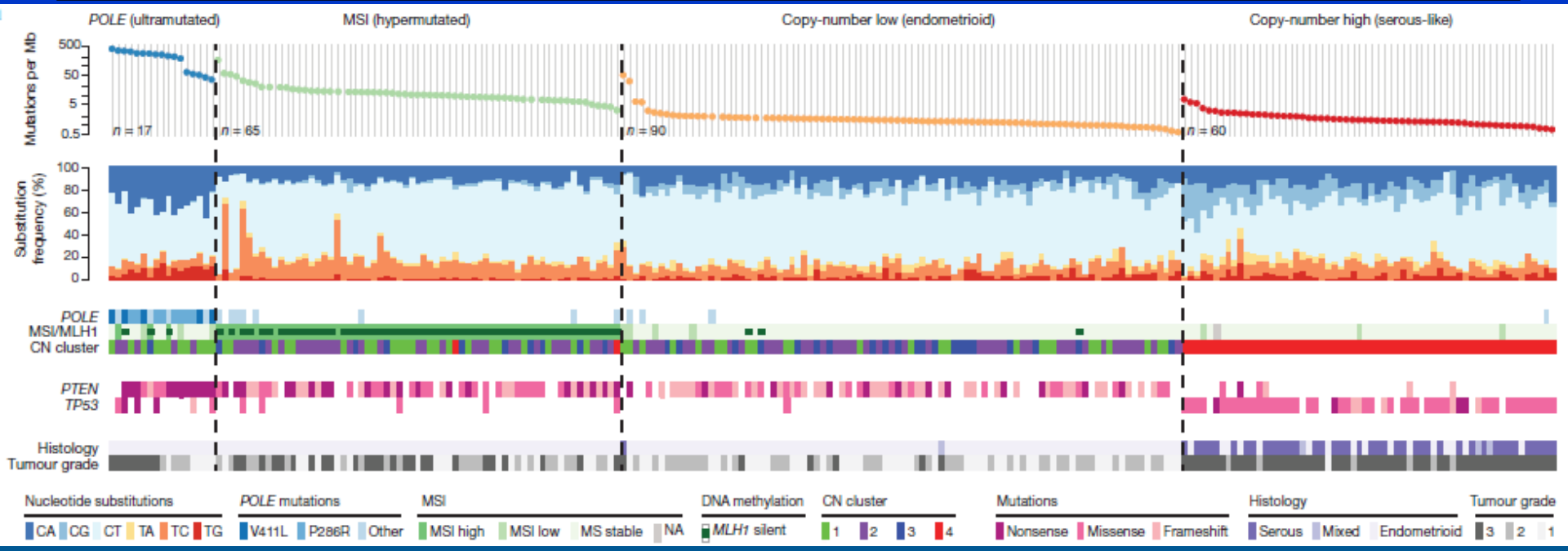
Randall, et al. *J Clin Oncol* 24:36-44, 2006

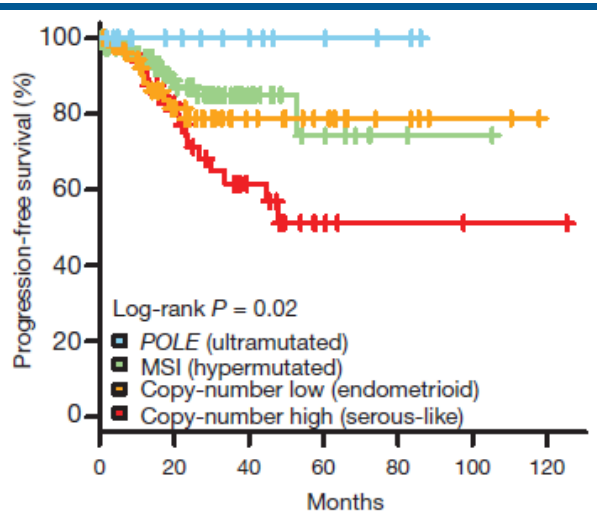
GOG122: Subset Analysis (OS)

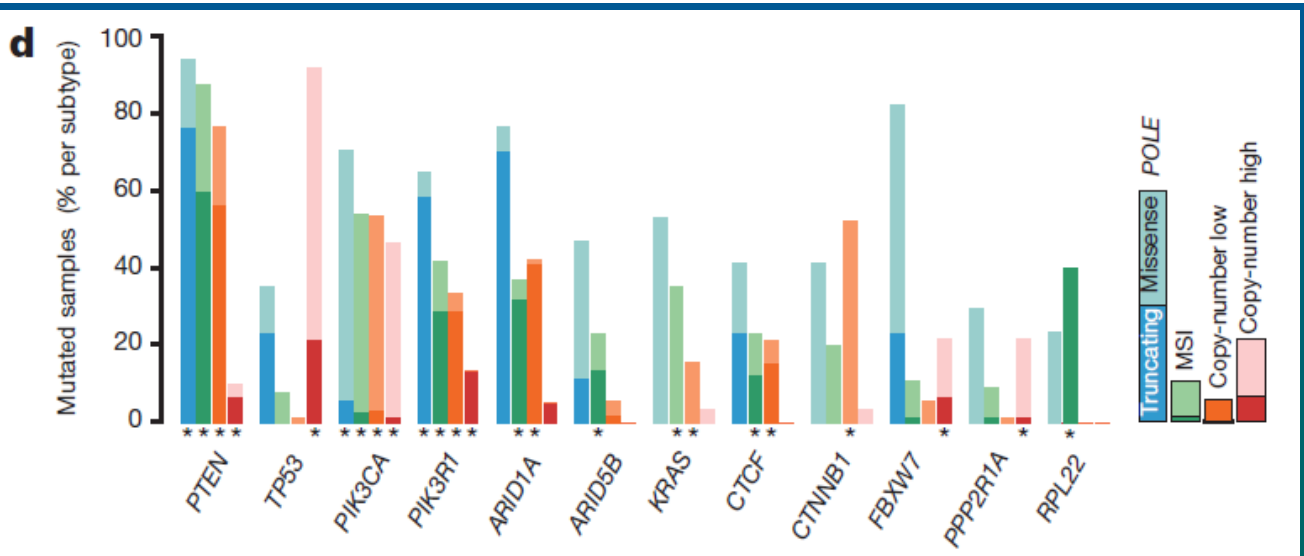


Randall, et al. *J Clin Oncol* 24:36-44, 2006

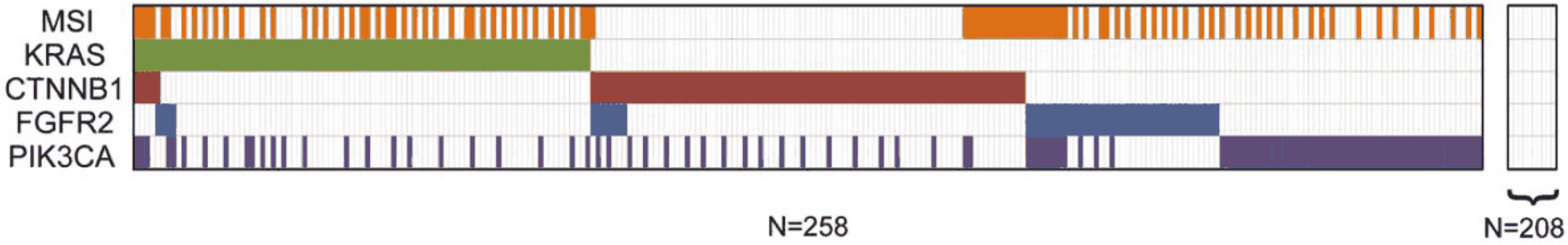
Targeting Endometrial Cancer: TCGA

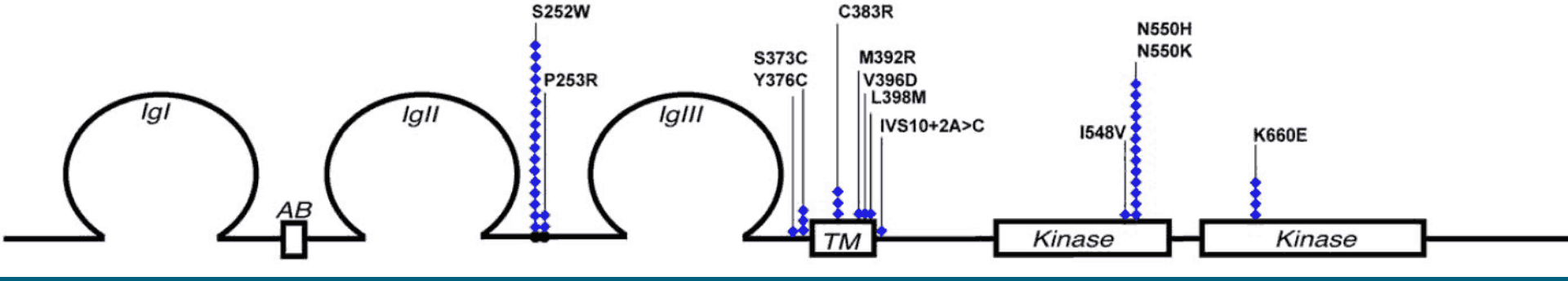






FGFR2 Mutations in Endometrial Ca





See Oral Presentation LBA27 - Phase 2 study of second-line dovitinib (TKI258) in patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or -nonmutated advanced and/or metastatic endometrial cancer G Konecny, et al

Byron SA, et al. *PLoS ONE* 7: e30801, 2012

Endometrial Cancer: Phase II Studies

Agent (Study Group)	Response Data CR/PR/SD/N (RR%)	PFS	@6m	Reference
Fulvestrant (GOG 188)	0/0/4/22 **(0%, ER-)** 1/4/9/31 **(16.1%, ER+)**			Covens AL, et al. Gynecol Oncol 2011;120:1185-8
Fulvestrant (AGO)	0/4/8/35 **(11.4%, ER+)**			Emons G, et al. Gynecol Oncol 2013;129:495-9
Bevacizumab (GOG 229E)	1/7/26/53 **(15.1%)**	4.2 m	35.8%	Aghajanian C, et al. J Clin Oncol 2011;29:2259-65
Brivanib (GOG 229I)	1/7/12/43 **(18.6%)**	3.6 m	27.9% 3/32 FGFR2 mut+ (non-responders)	Powell MA, et al. Int J Gynecol Cancer 2012:22(s3:E115)
Cediranib (GOG 229J)	0/6/18/48 **(12.5%)**	3.6 m	33.3%	Bender DP, et al. GOG
Nintedanib (GOG 229K)	0/3/11/32 **(09.4%)**		21.9%	Dizon D, et al. SGO 2014 (A133)

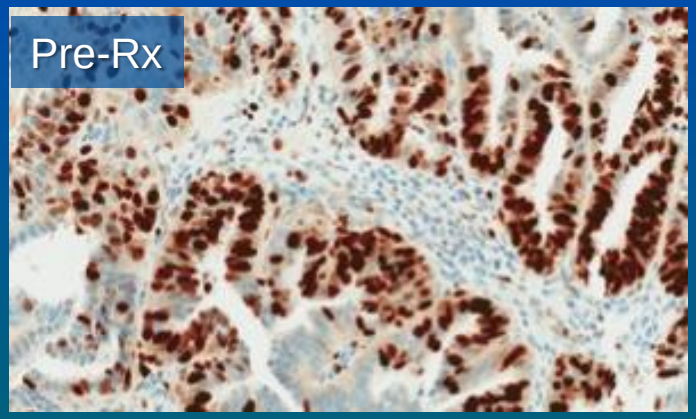
Metformin Translational Window Study

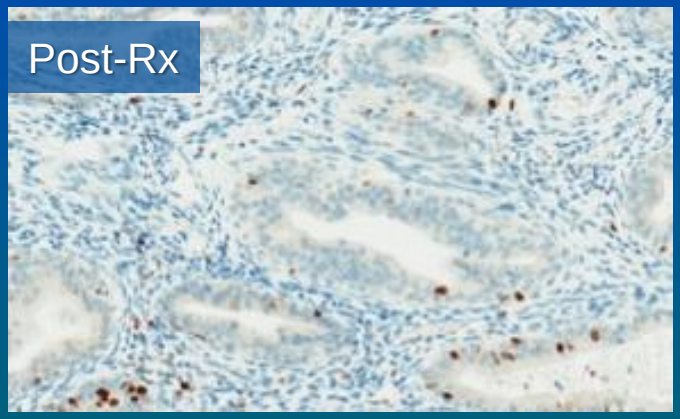
New Diagnosis BMI ≥30
Endometrioid Histology

→ Metformin
850 mg QD

→ Definitive Surgery
(within 7-28 d)

- Tissue microarrays pre- and post-metformin
- Immunohistochemistry Ki-67, pAMPK, mTOR, pAKT, pS6, ER/PR
- Metabolomics panel (serum and tissue)





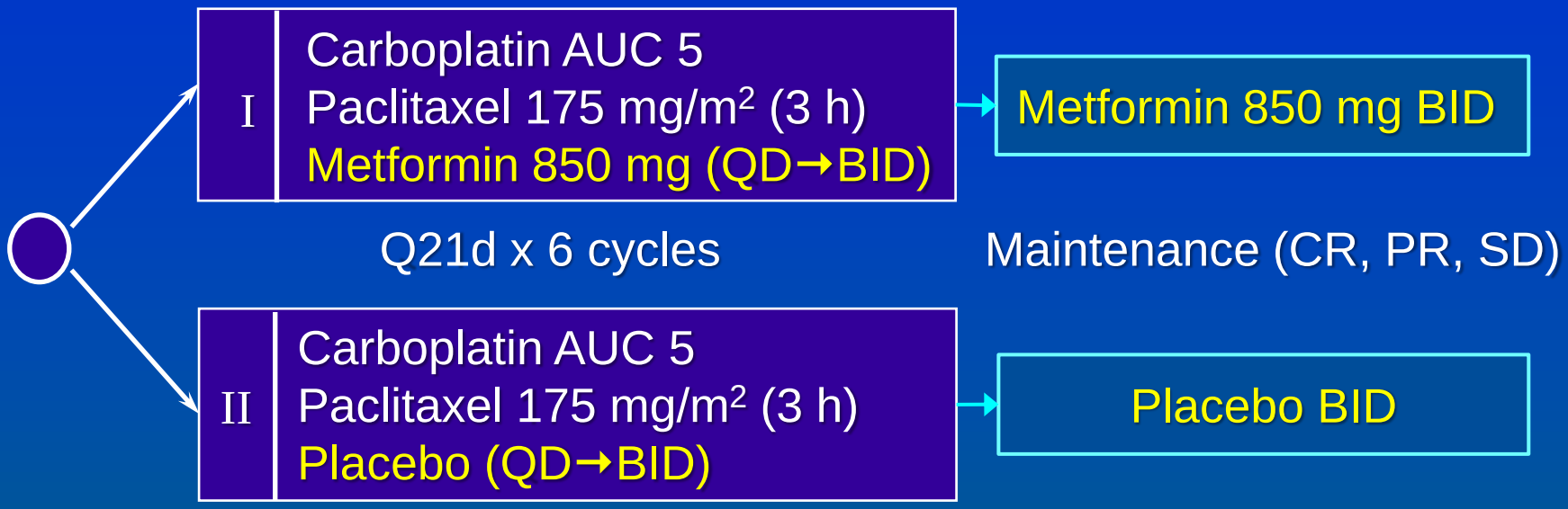
Mean Ki-67 Index
Pre-Rx: 39.5
Post-Rx: 27.7

(n = 20)

IHC Molecular Markers (Pre- and Post-Rx)					
pAMPK	↓60.3%	pAKT	↓44.2%	pS6	↓51.2%
p4EBP1	↓74.7%	ER	↓65.7%	PR	(NC)

Schuler KM, et al. SGO 2014 (Abstract 8)

GOG286B: Chemo +/- Metformin



- Stg III-IVA (measurable) and Stg IVB or recurrent
- Integrated Phase II (PFS) → Phase III (OS)
  - 240 pts phase II (60 events, PFS HR 0.76)
  - 540 pts phase III (OS HR 0.76)

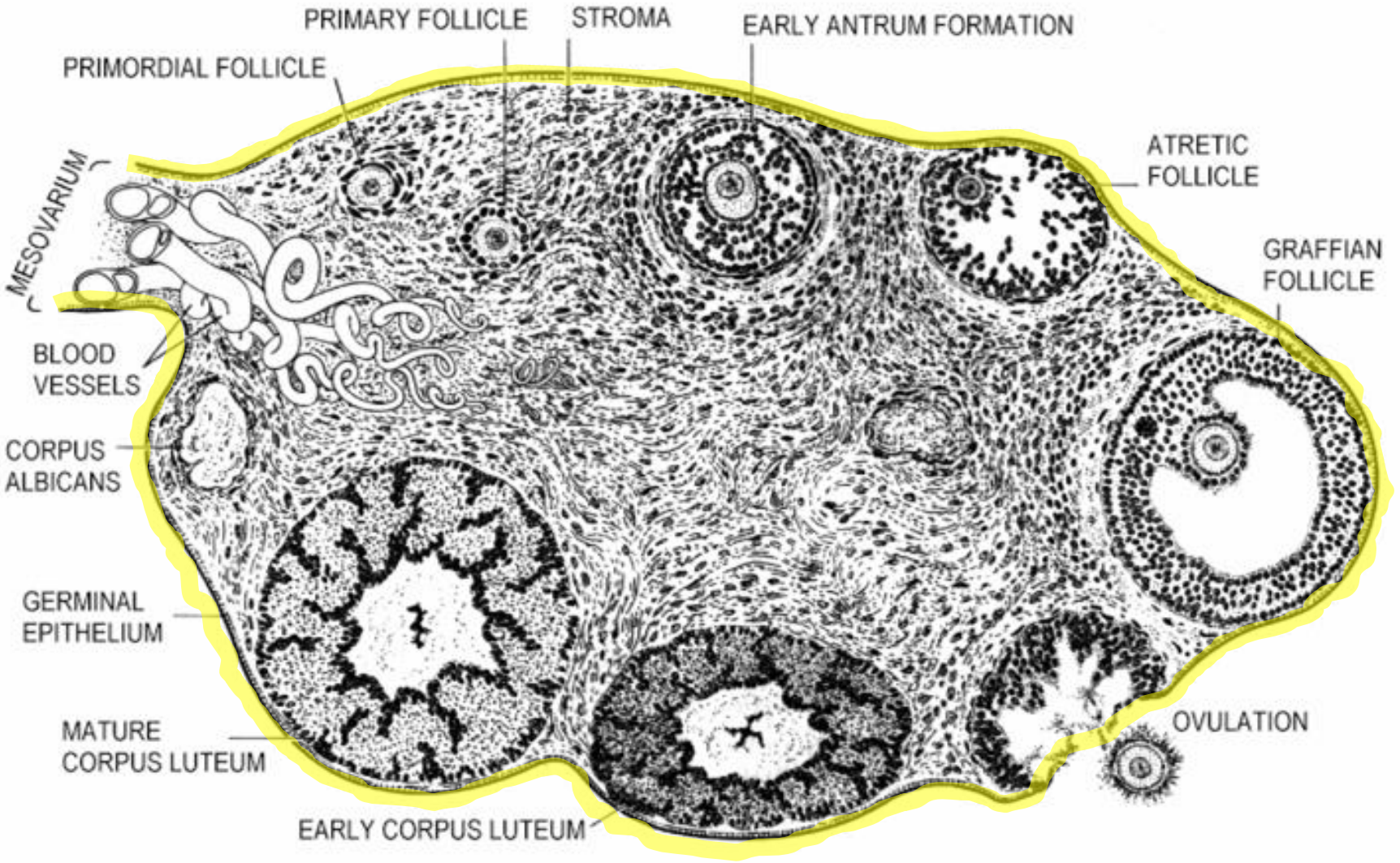
Open: 17-Mar-2014
Closed: (ongoing)
Accrual: 540 (Phase II + III)

Bae-Jump V, et al. for GOG

Targeting Endometrial Cancer

- Screening and risk stratification, incorporating DNA-based cytology
- Recognize increasing incidence of high-grade advanced-stage cancers without bleeding (Type II)
- Expanded emphasis on minimally-invasive surgery and sentinel LN Bx
- Optimized multi-modality therapy for advanced disease
- Broaden MSI screening by tumor IHC and genomics for family risk management HNPCC (Type I > II)
- Incorporate screening of BRCA status (Type II)
- Obesity has become a targetable risk factor (Type I > II)
- Incorporation of metformin, targeting obesity-associated growth factors and signal transduction pathways

Targeting Ovarian Cancer



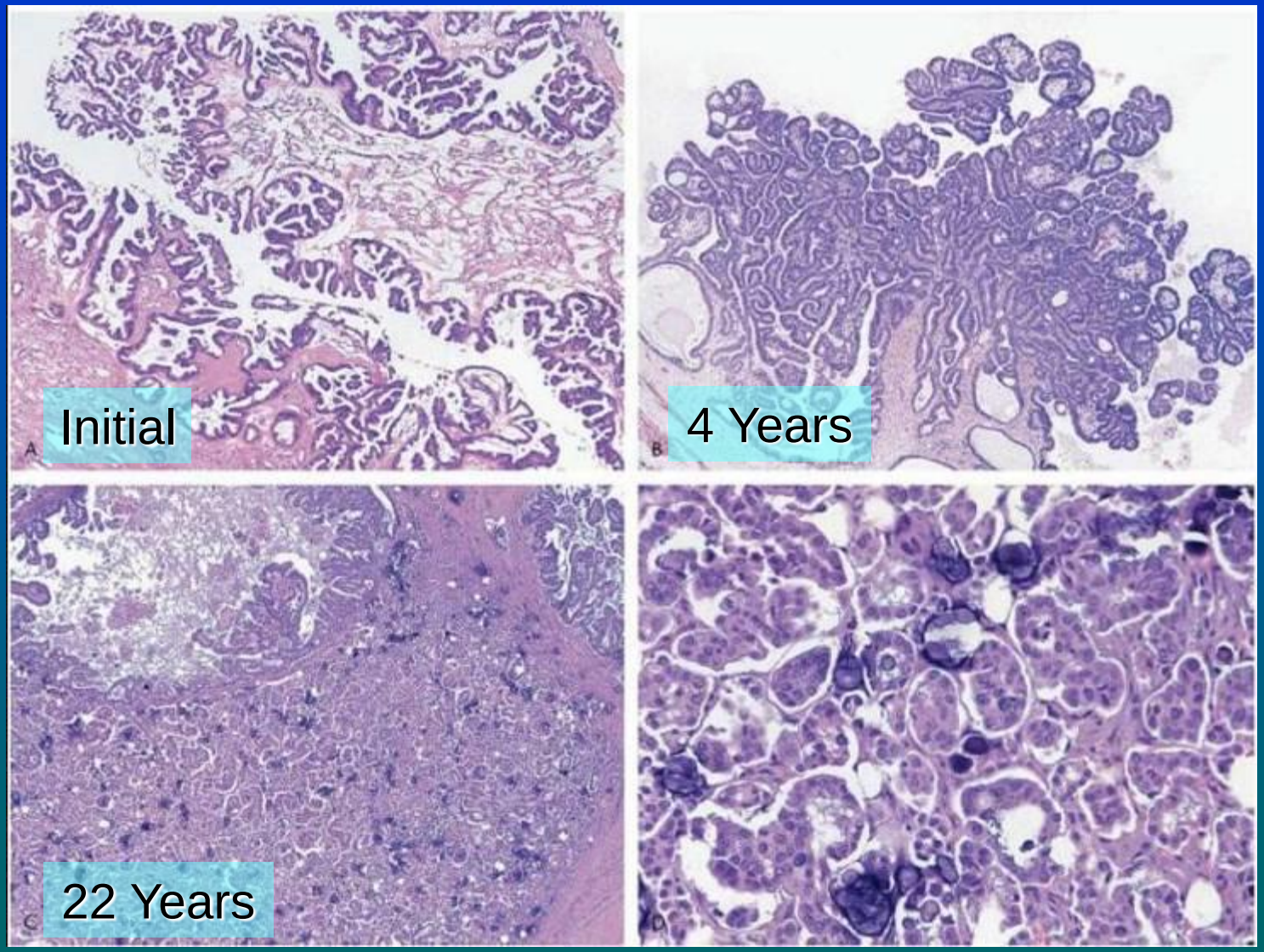
Modified from Yen and Jaffe, Reproductive Endocrinology, 1986

Targeting Ovarian Cancer: Subtypes

	HGSC	CCC	EC	MC	LGSC
Percentages: **FIGO I-II** **FIGO III-IV**	 39% 86%	 33% 2%	 22% 7%	 5% 2%	 1% 3%
Genetic Risk	BRCA1/2	HNPCC	HNPCC	None known	None known
Other Risk Factors	↓ Risk with OC, pregnancy	None known	↓ Risk with OC, ↑ Risk with HRT	None known	None known
Precursors	STIC	Endometriosis	Endometriosis	Unknown	SBT
Presentation	Ascites, GI sxs	Adnexal mass	Adnexal mass	Adnexal mass	GI sxs
Pattern of Spread	Peritoneal, nodal	Peritoneal, nodal, distal	Peritoneal, nodal, distal	Peritoneal +/- Pseudomyxoma	Peritoneal, nodal
Chemotherapy Response	Sensitive, then resistant	Resistant	Sensitive	Resistant	Resistant
Molecular Genetics	p53, BRCA1/2, PI3K, HRD	PI3K, ARID1A, MSI	PTEN, β catenin, ARID1A, MSI	KRAS, HER2	BRAF, KRAS, NRAS
Targets	PARP, Angiogenesis	Angiogenesis	ER, PR, mTOR	HER2/neu	BRAF, KRAS MEK/ERK

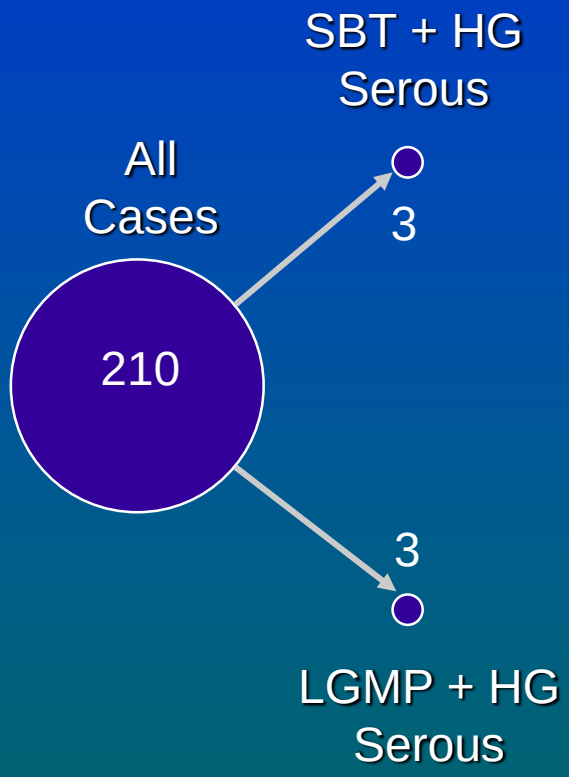
Modified from: Bookman MA, et al., *J Natl Cancer Inst* 2014;106 PMID 24627272

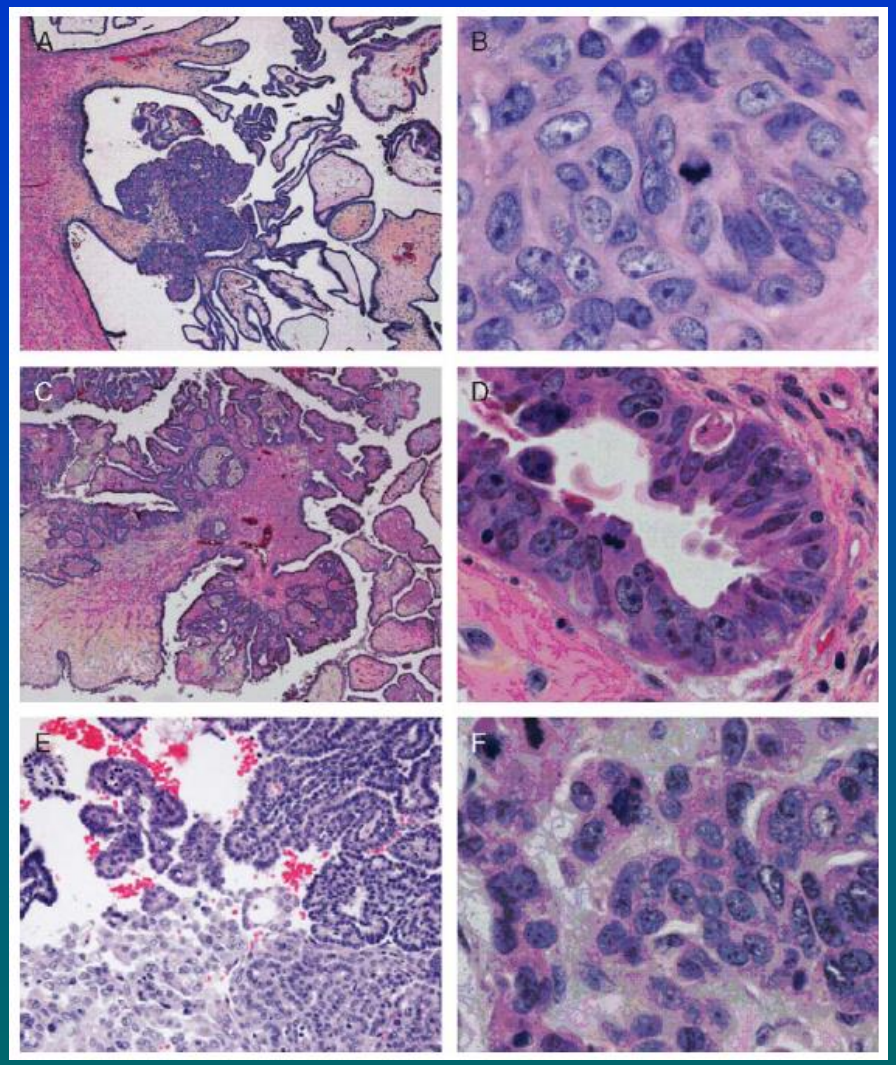
LGSC: Recurrence and Transformation



T Longacre et al. , *Am J Surg Pathol, 29:707-23, 2005*

LGSC: High-Grade Transformation





K-RAS(+)
B-RAF(wt)
p53 (wt)

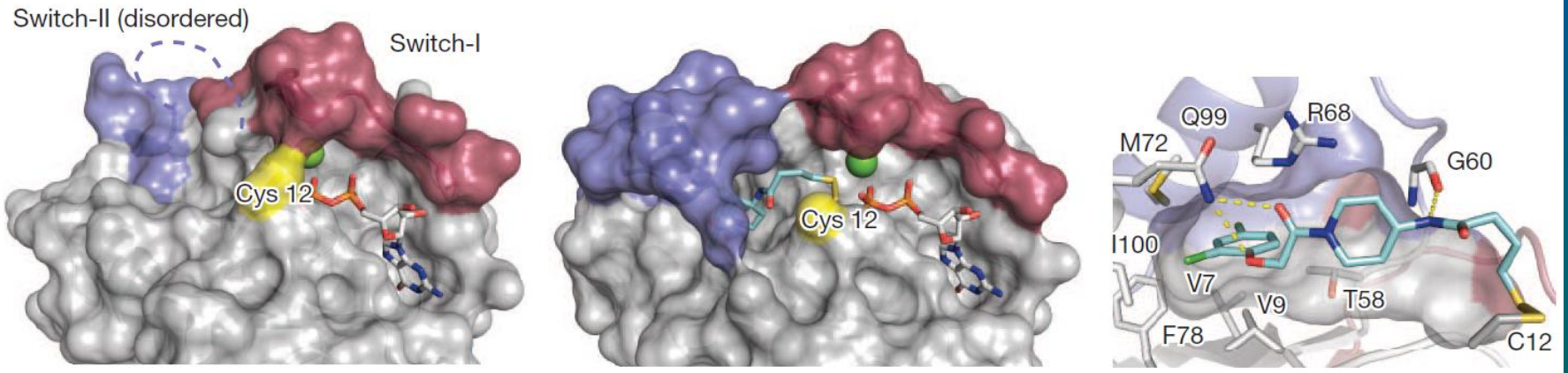
K-RAS(+)
B-RAF(wt)
p53 (wt)

K-RAS(wt)
B-RAF(wt)
p53 (wt)

Dehari R, et al. *Am J Surg Pathol* 2007;31:1007–1012

Targeting LGSC: Predictions

- Surgical resection will remain the best curative intervention for SBT and LGSC (primary and recurrent)
- LGSC can progress to HGSC, retaining the molecular characteristics of LGSC (p53 wild-type with mutations in K-RAS or B-RAF)
- Network targeting of activated MEK/ERK can achieve short-term responses, but targeting mutated K-RAS or B-RAF could prove more effective
- Broad-spectrum inhibitors of K-RAS are not available, and would likely have unacceptable host toxicity
- Tumor-specific (mutation-specific) inhibitors of K-RAS are being developed



Targeting K-Ras (G12C). Modified from: Ostrem JM, et al. *Nature* 503:548-51, 2013

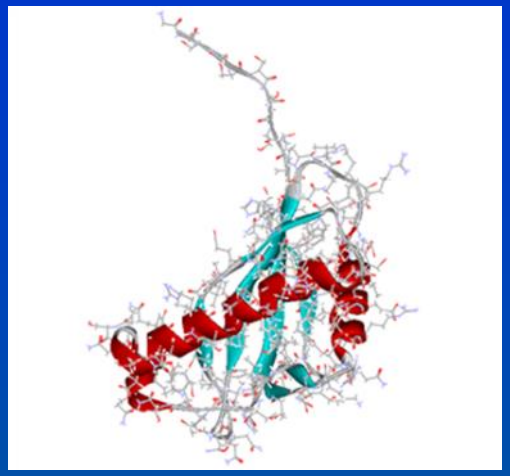
Targeting HGSC: Screening

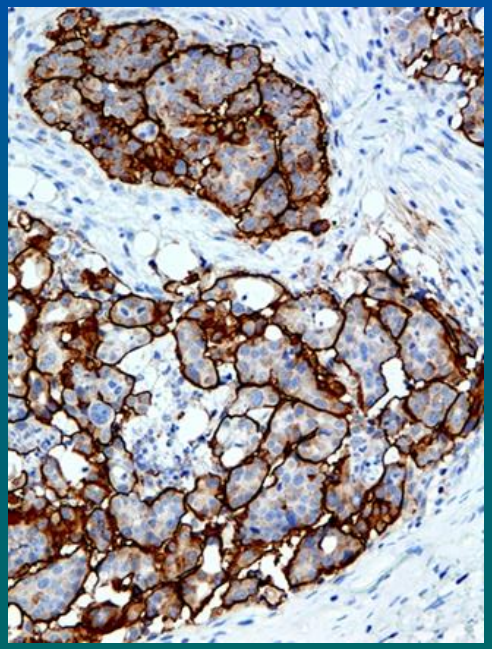
- NCI PLCO (78,216 ♀) annual CA125 and TVUS: Negative
- UKCTOCS trial (202,638 ♀) CA125 ROCA and TVUS: Primary Endpoint expected DEC 2014
- Multi-Marker Panels (beyond CA125): Minor Impact
- Exponential Technical Advances in Sensitivity…
  - Ovarian micro-laparoscopy and cytologic sampling
  - Ovarian DNA from cervical smear or blood
  - High-resolution external imaging…

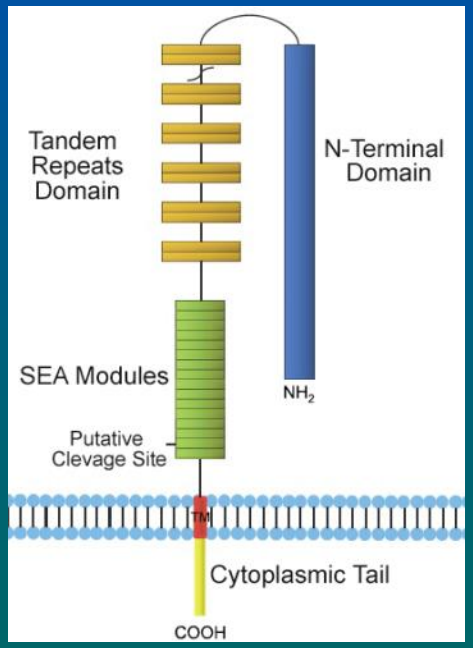
One example: Ferromagnetic nanoparticles and superconducting quantum interference device (SQUID), suggested by Kenning GG , et al. 2003

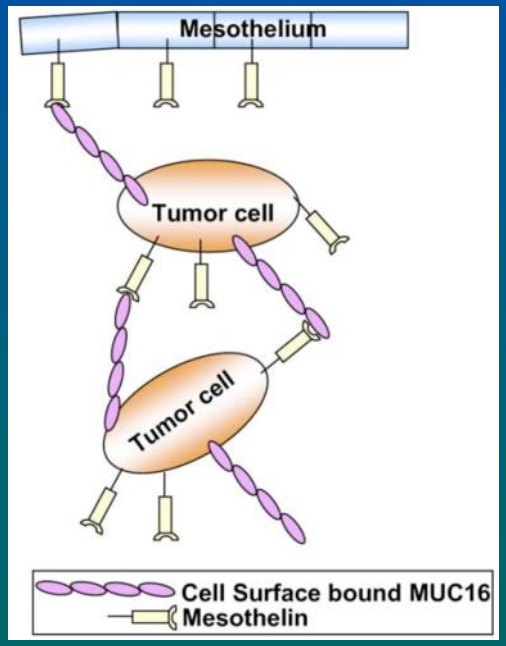
Targeting HGSC: CA125 and MUC16

- High MW tumor Ag, murine Ab OC125 (cloned 1981)
- Heavily glycosylated mucin , MUC16 gene, provides hydrophilic barrier on cornea, respiratory tract, and female reproductive organs
- Binds mesothelin, promotes peritoneal implantation
- Contributes to tumor immune evasion
- No better serum marker identified (> 30 years)



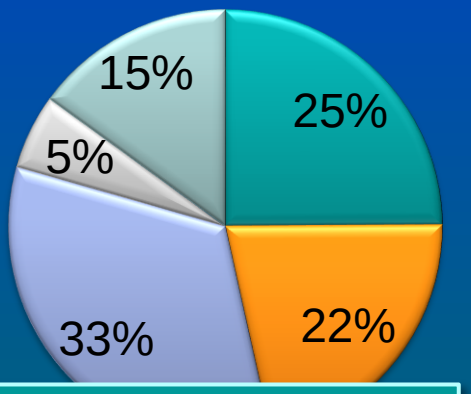






EOC: Histology by Stage

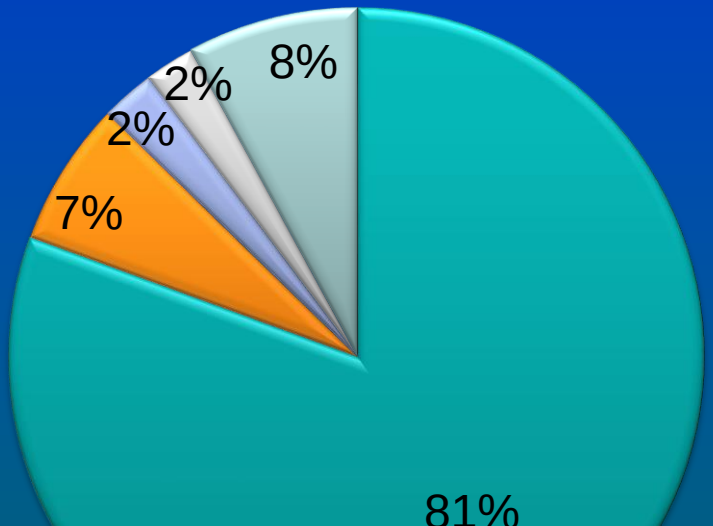
Stage I-II (Early)



Serous
Endometrioid
Clear Cell
Mucinous
Mixed-Other

25% HGSC
25% recurrence

Stage III-IV (Advanced)



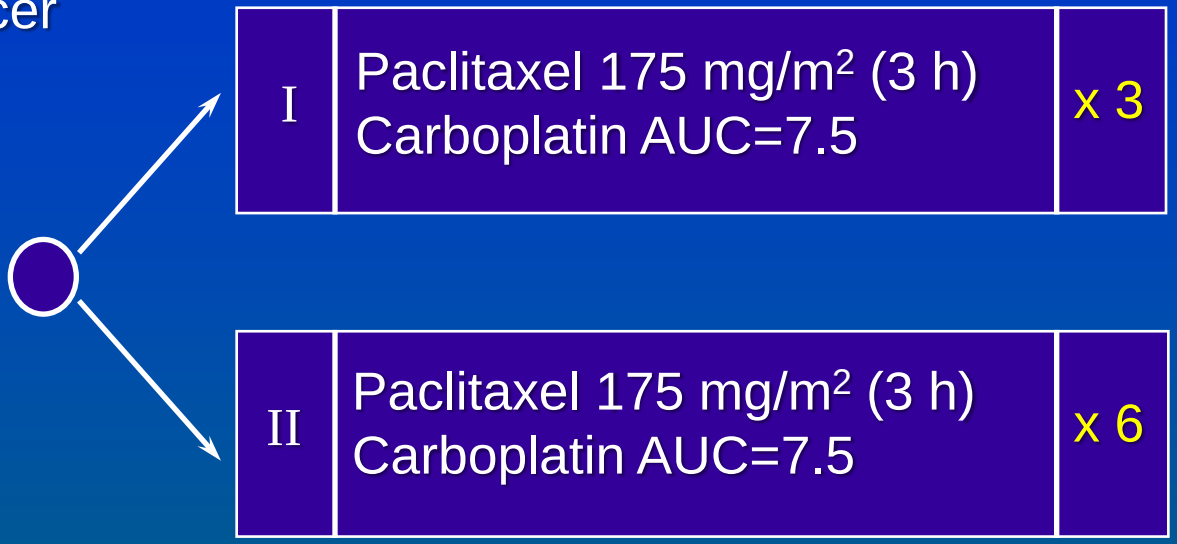
81% HGSC
80% recurrence

Bell JG. *Gynecol Oncol* 102:432-9, 2006

Bookman MA. *J Clin Oncol* 27:1419-25, 2009

GOG157: Ovarian (Early-Stage)

- Epithelial Ovarian Cancer
- Stage IC/II any grade
- Stage IA/B high grade
- No prior therapy

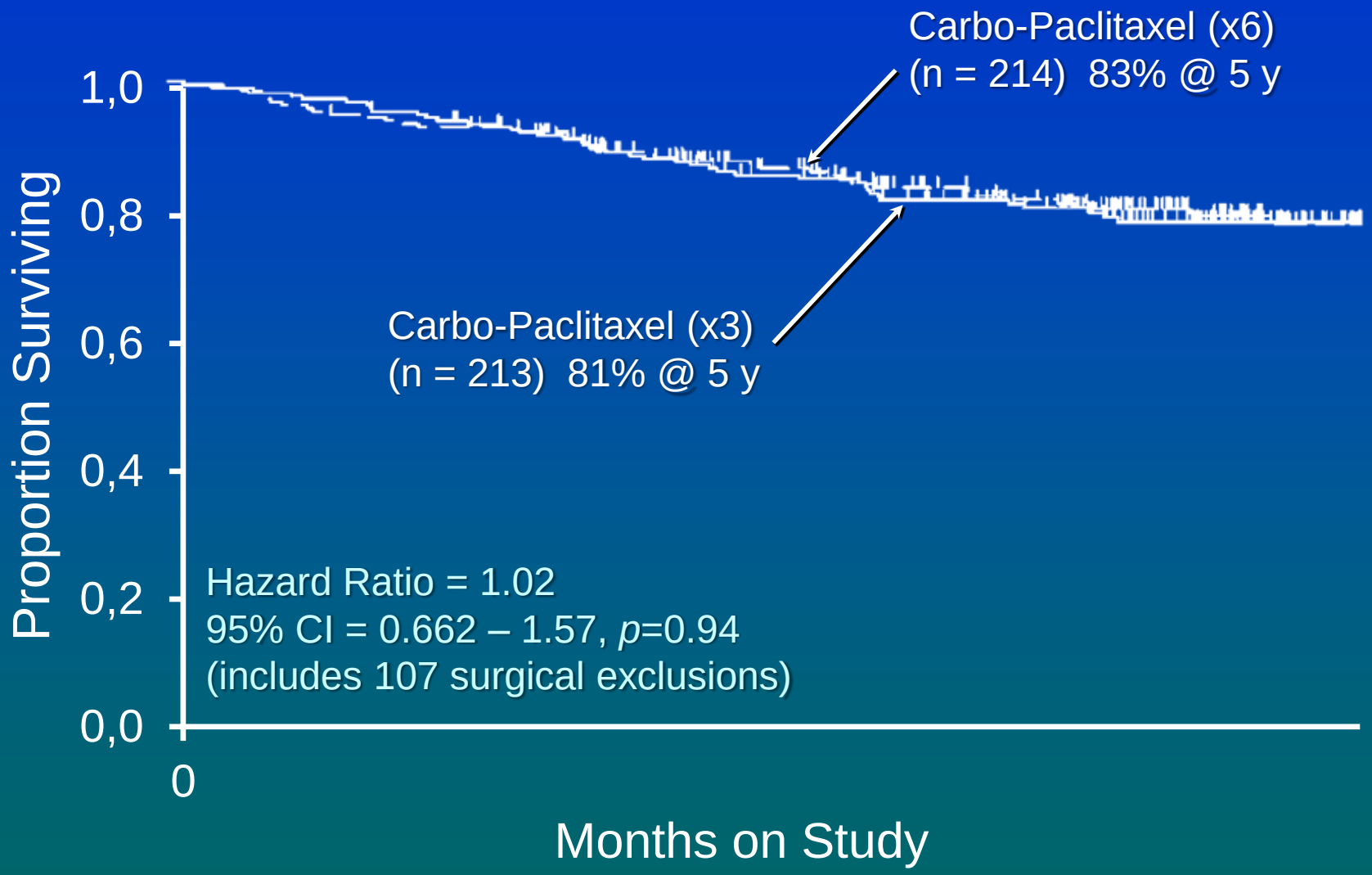


- Only 70% met eligibility criteria (133 excluded)
- 107/457 (23%) were incompletely staged
- Hematologic toxicity and neuropathy increased with 6 cycles

Open: 20-Mar-95
Closed: 25-May-98
Accrual: 457 pts

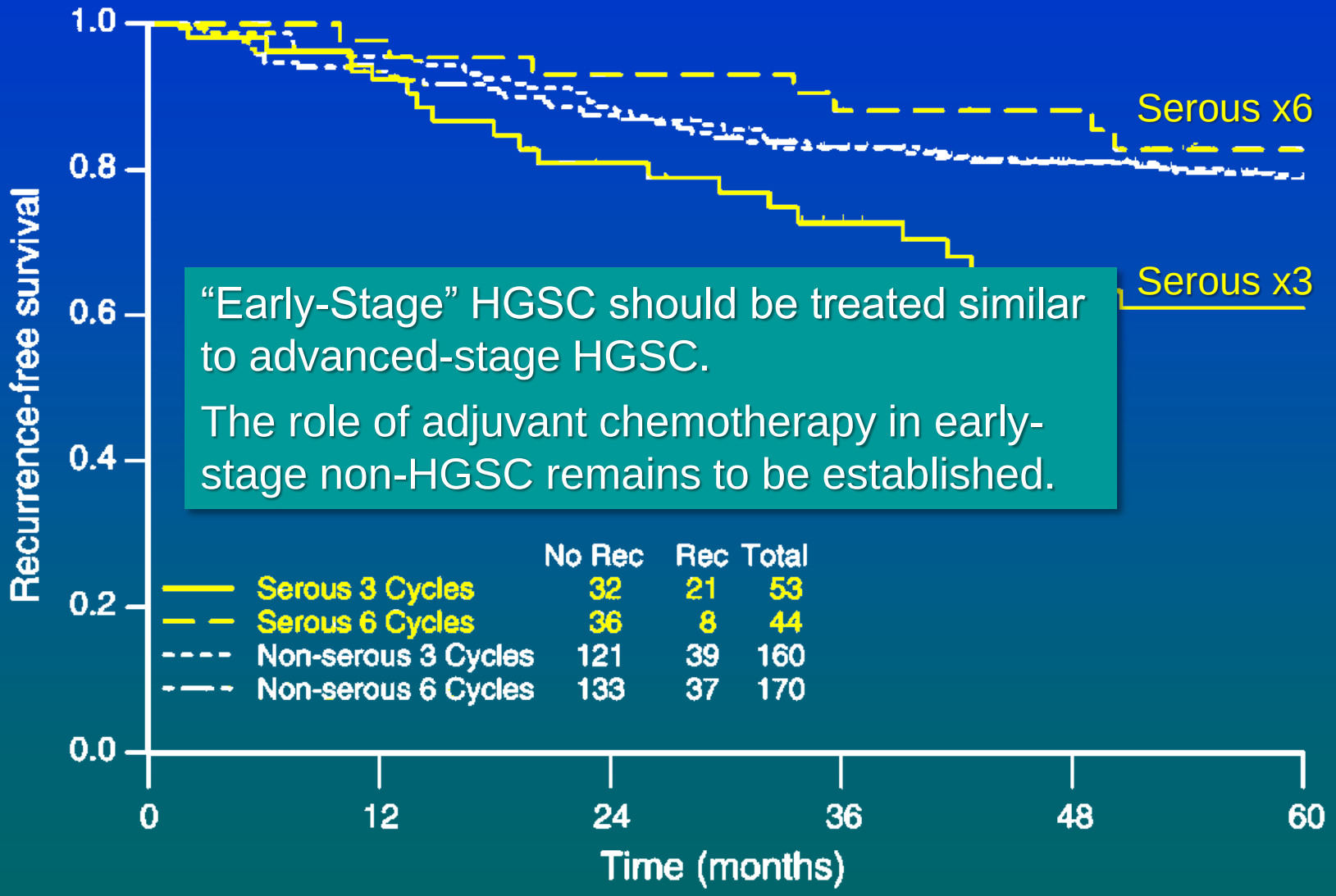
Bell JG, et al. *Gynecol Oncol* 102:432-9, 2006

GOG157: Ovarian (Early-Stage)



Bell JG, et al. *Gynecol Oncol* 102:432-9, 2006

GOG0157: Histologic Subsets



"Early-Stage" HGSC should be treated similar to advanced-stage HGSC.

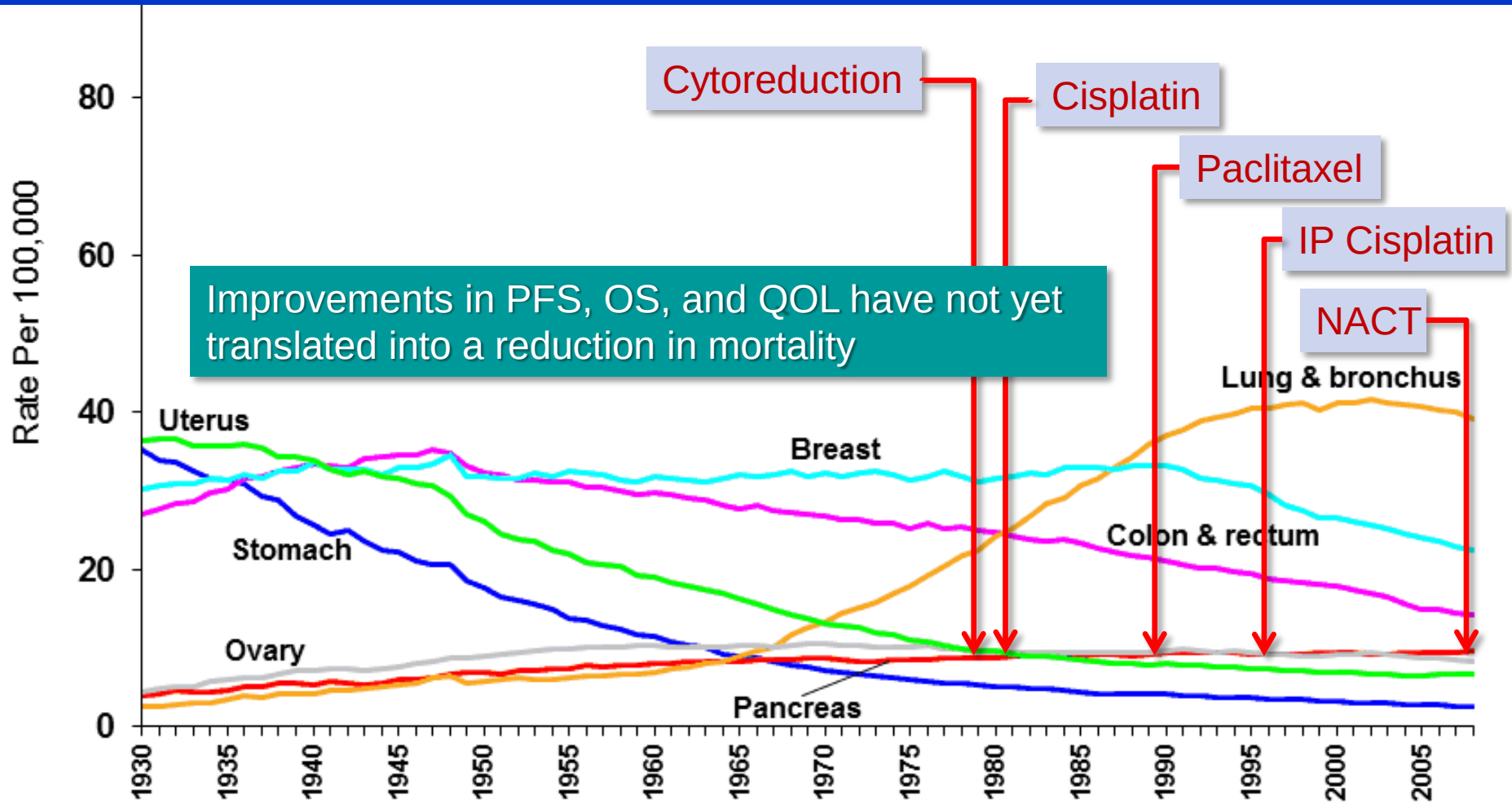
The role of adjuvant chemotherapy in early-stage non-HGSC remains to be established.

Chan JK, et al. *Gynecol Oncol* 116:301-6, 2010

HGSC: Screening & Prevention

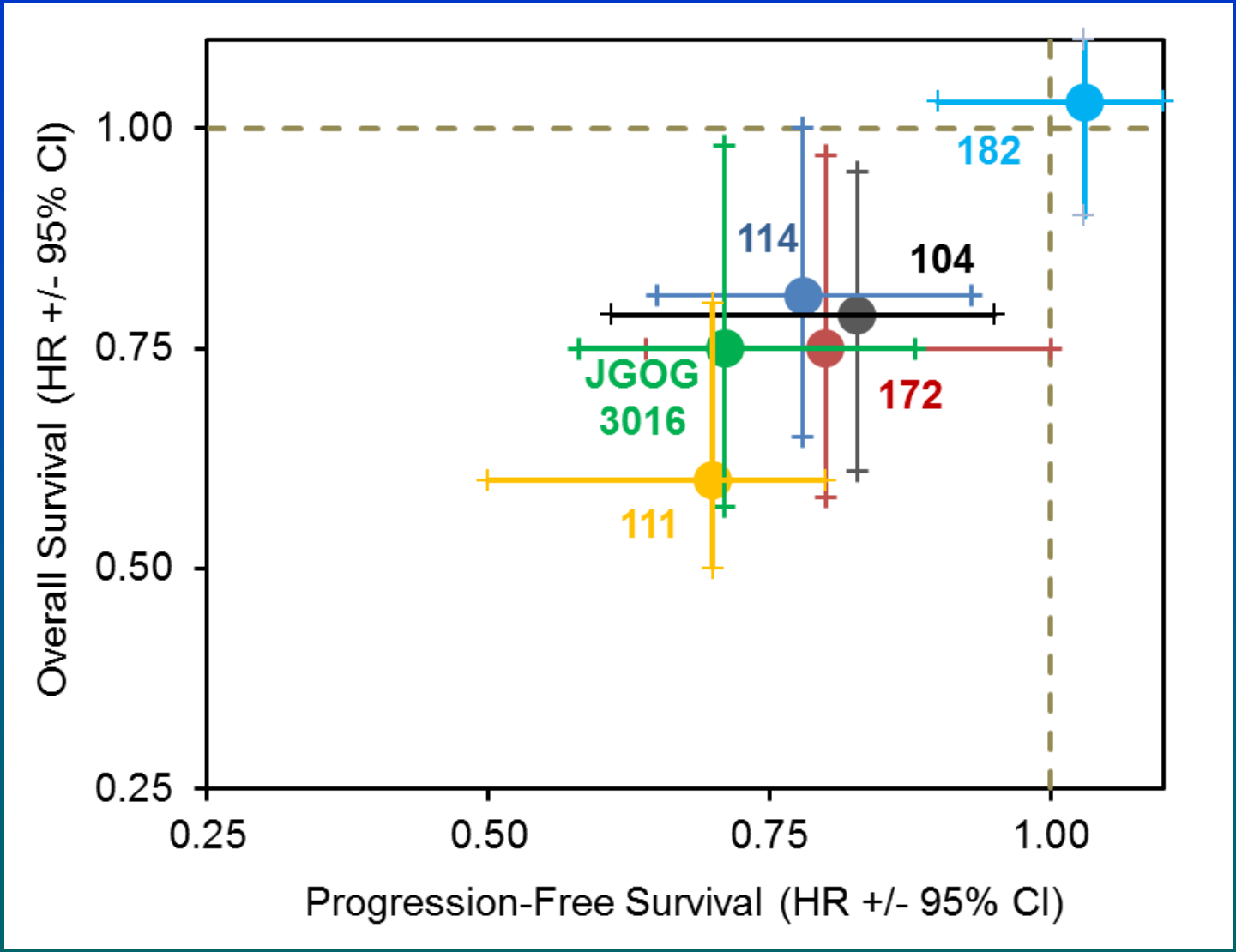
- Multi-platform molecular analysis will identify more patients at risk, based on inherited and non-inherited mutations, and promote tailored risk reduction strategies.
- Protective mechanisms associated with oral contraceptives and parity will be elucidated, promoting more effective chemoprevention
- Screening with CA125 and TVUS is unlikely to impact mortality
- Technology will enhance sensitivity for screening, but the biology of HGSC will challenge even the most sensitive approaches
- Understanding the essential roles of CA125 will identify new targets and interventions
- Salpingectomy (without oophorectomy) could prevent some cancers, especially in high-risk populations with germline BRCA1/2 mutations, but will prove difficult to evaluate in a randomized trial

Cancer Death Rates: (US 1930-2008)*



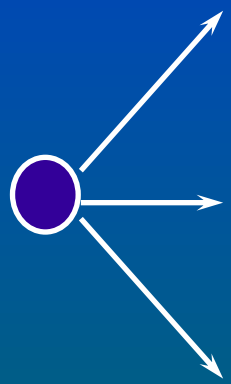
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2008, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention.

Targeting HGSC: IP Chemotherapy



GOG0252: IP Therapy

- Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer
- Optimal and Suboptimal Disease (through April 2011)
- Primary Endpoint: PFS (Analysis OCT 2014)



IV Carbo	I	Carboplatin AUC=6 (IV) Paclitaxel 80 mg/m^2 IV (d1,8,15) Bevacizumab (C2-6)	Bevacizumab q21d x 16
IP Carbo	II	Carboplatin AUC=6 (IP) Paclitaxel 80 mg/m^2 (d1,8,15) Bevacizumab (C2-6)	Bevacizumab q21d x 16
IP Cisplatin	III	Cisplatin 75 mg/m^2 (IP) Paclitaxel 135 mg/m^2 (d1, 3h) Paclitaxel 60 mg/m^2 (d8, IP) Bevacizumab (C2-6)	Bevacizumab q21d x 16

Open: 27-Jun-2009
Closed: 29-Oct-2011
Accrual: 1560 pts (250 suboptimal)

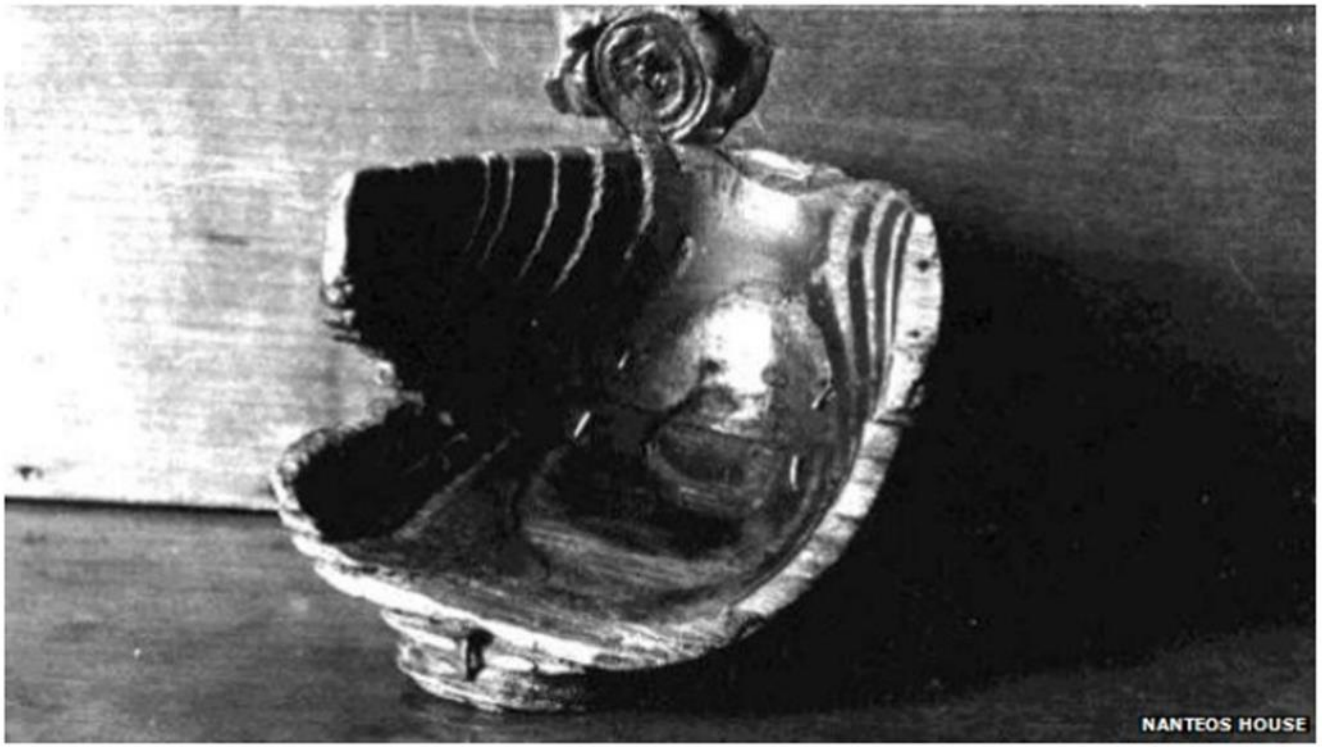
Walker J. for GOG, *pending*

HGSC: Surgery and Primary Therapy

- With improved diagnostics, high-resolution functional imaging, and intra-operative detection, the majority of patients will achieve optimal (R0) cytoreduction using a minimally-invasive approach
- Patients with high-volume disease and comorbidities will undergo molecular risk-profiling to facilitate selection of neoadjuvant chemotherapy and potential interval cytoreductive surgery
- Carboplatin with weekly dose-dense paclitaxel is a reasonable standard-of-care, and a point-of-reference for future randomized trials
- The modest prolongation of PFS associated with front-line anti-angiogenic agents (after cytoreductive surgery) can likely be offset by optimized chemotherapy
- Benefits associated with IP chemotherapy will be offset by incorporation of targeted agents and optimal dosing of systemic chemotherapy

“The Holy Grail” of Ovarian Cancer

Police raid Crown Inn pub in Lea in 'Holy Grail' relic hunt



The Nanteos Cup was stolen from the house of a seriously ill woman while she was in hospital

Police raided a village pub searching for a stolen Holy Grail relic but only found a salad bowl.

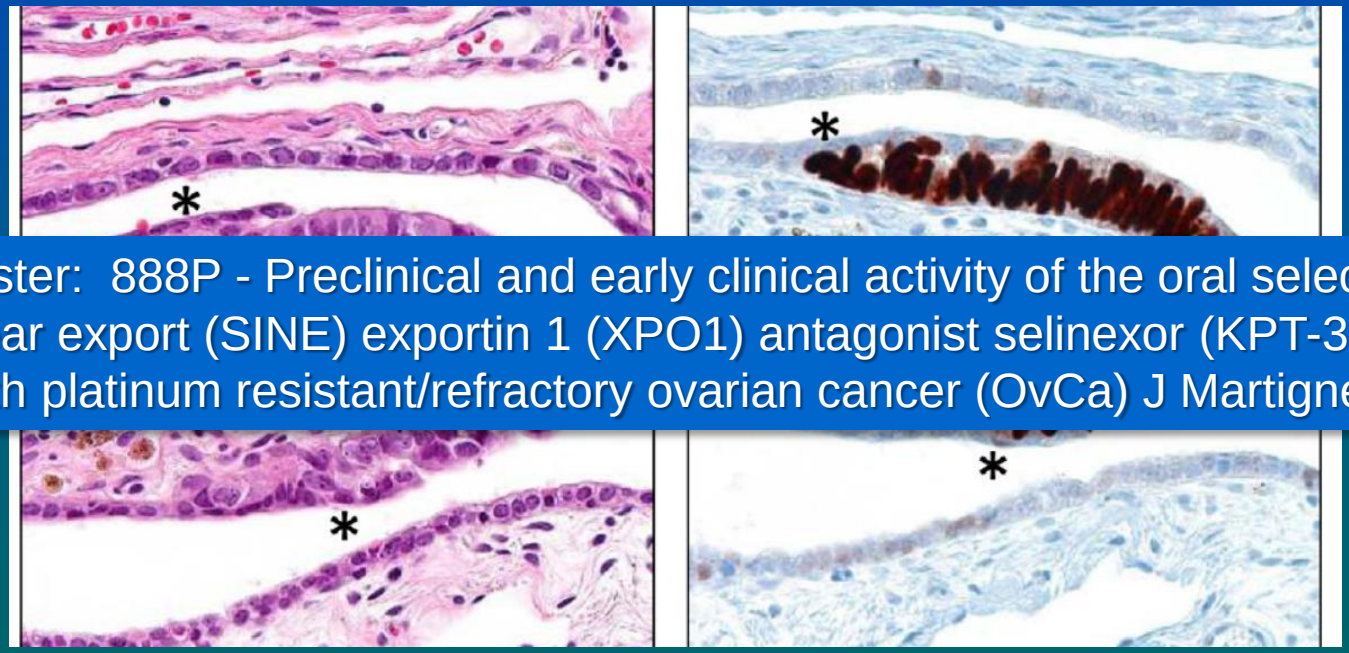
A team of 12 West Mercia Police officers searched the Crown Inn in Lea, Herefordshire, for the **Nanteos Cup, which was once housed in Aberystwyth.**

Related Stories

Police in hunt for the 'Holy Grail'

Targeting HGSC: TP53

- TP53 loss associated with defective DNA damage detection and apoptotic signaling. Early initiating event through mutation, deletion, LOH
- Targeting strategies in cervical cancer (non-mutated TP53, HPV-E6 peptide, MDM2/4 regulation) not directly applicable in HGSC. Await novel strategies to suppress mutated TP53 and/or restore activity of TP53 and other tumor suppressor genes.



See Poster: 888P - Preclinical and early clinical activity of the oral selective inhibitor of nuclear export (SINE) exportin 1 (XPO1) antagonist selinexor (KPT-330) in patients (pts) with platinum resistant/refractory ovarian cancer (OvCa) J Martignetti, et al.

STIC. High magnification, H&E stain (left) and IHC stain for p53 (right).

Kurman RJ and Shih I-M, *Am J Surg Pathol* 2010;34:433-43

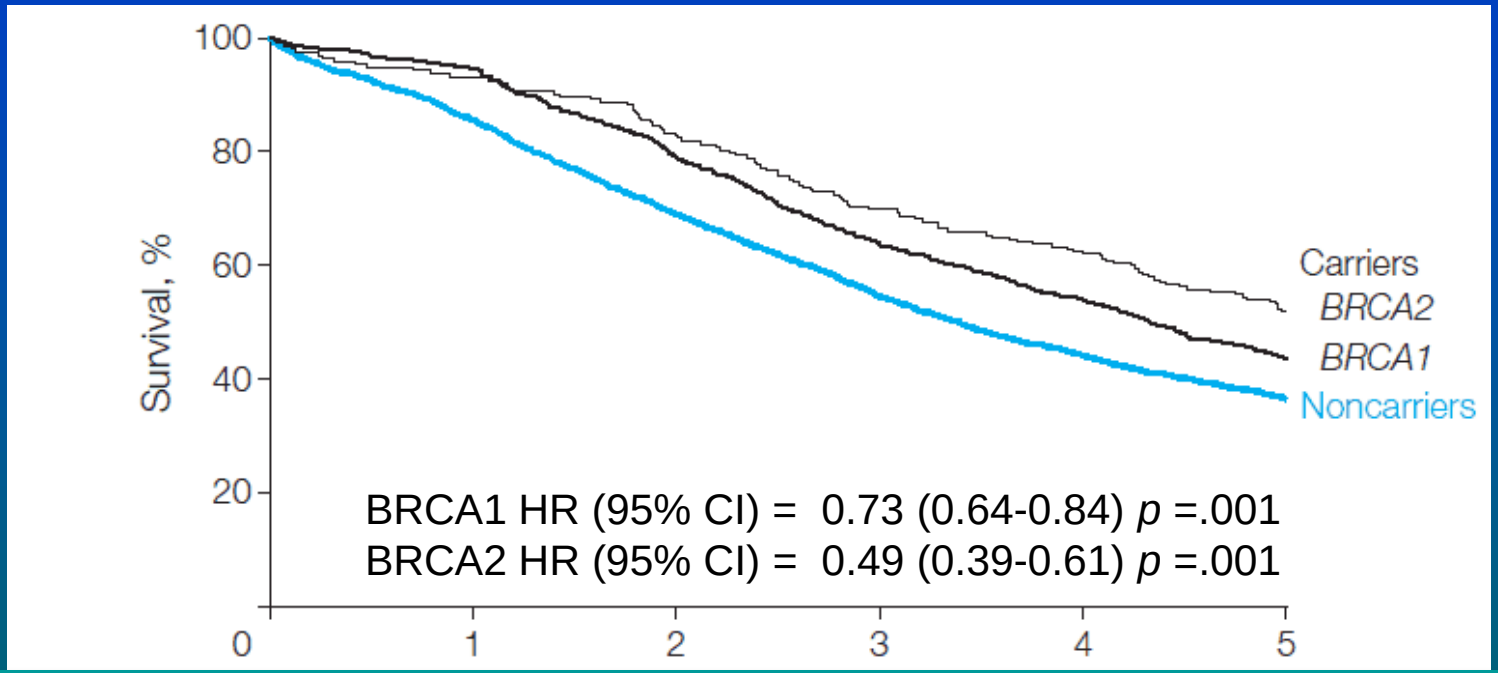
Targeting HGSC: DNA Repair

- Homologous Recombination Deficiency (HRD)
  - Multiple genes involved in error-free DNA repair
  - Molecular basis for HRD detected in over 50% of HGSC
  - Prominent role for BRCA1/2 (germ line and somatic)
  - Synthetic Lethal Strategy with PARPi exposure
  - Secondary “restorative” mutations in BRCA1/2 can overcome PARPi
  - Potential interaction with chemotherapy, angiogenesis, and signal transduction pathways
  - Ongoing need for better preclinical models, such as patient derived xenografts.

See Poster: 906P - Microfluidic maintenance of ovarian tumour biopsies for the study of hypercoaguability during chemo

Impact of Germline BRCA1/2 Mutations

- Pooled analysis, 26 observational studies, 1213 EOC Pts with germline BRCA1 (n=909) or BRCA2 (n=304) mutations, and 2666 non-carriers



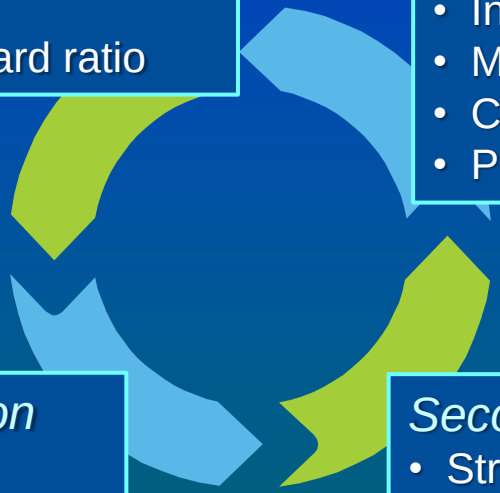
- Germline BRCA1/2 mutations are PROGNOSTIC, and identify a population with improved outcomes, regardless of treatment
- Mutations are also PREDICTIVE for response to DNA-targeted chemotherapy (in general), and PARP inhibitors (in particular)

Bolton KL, et al. *JAMA*. 307:382-390, 2012

Phase III Design

Initial Design Parameters
- Scientific-Clinical Hypothesis
- Superiority *vs* Non-Inferiority
- Selection of Primary Endpoint (PFS or OS)
- Historical reference data
- Targeted improvement and hazard ratio

Budgetary Considerations
- Regulatory *vs* non-regulatory
- Size and duration of study
- Monitoring requirements
- Independent DSMB
- Independent response evaluation
- Medication production and supply
- Coverage for tests/procedures
- Potential for Return on Investment

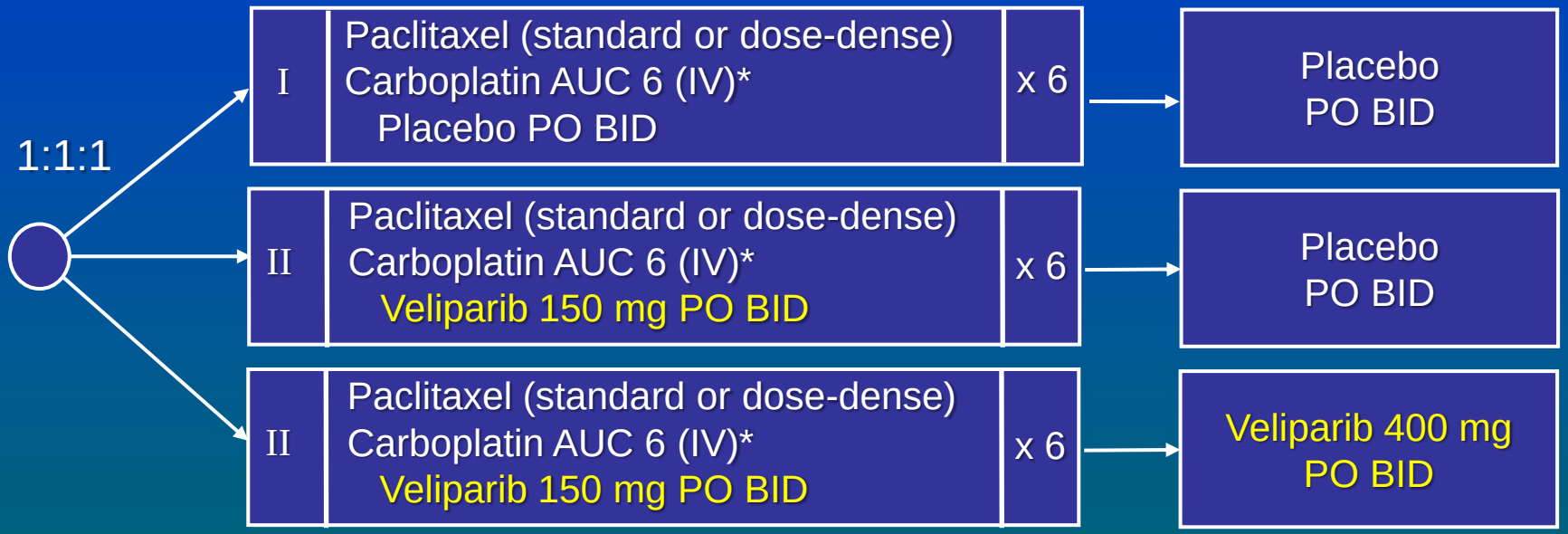


Sample Size Determination
- Anticipated rate of accrual
- Anticipated event rate
- Proposed α (0.05) and β (0.80)
- One-sided or two-sided analysis
- Interim analysis for futility
- Interim analysis for efficacy

Secondary Endpoints
- Stratification and subset analysis
- Incorporation of biomarkers
- Cost effectiveness, QOL

GOG3005: PARPi Primary Therapy & Maint

- High-grade extrauterine serous tumors, Stage I-C, II, III, IV
- Election for NACT-ICS and scheduling of paclitaxel (no IP therapy)
- Primary endpoint PFS: (1) Entire Population, (2) BRCA1/2 Population
- Stratifications: Stage, Residual Disease, NACT-ICS, Region



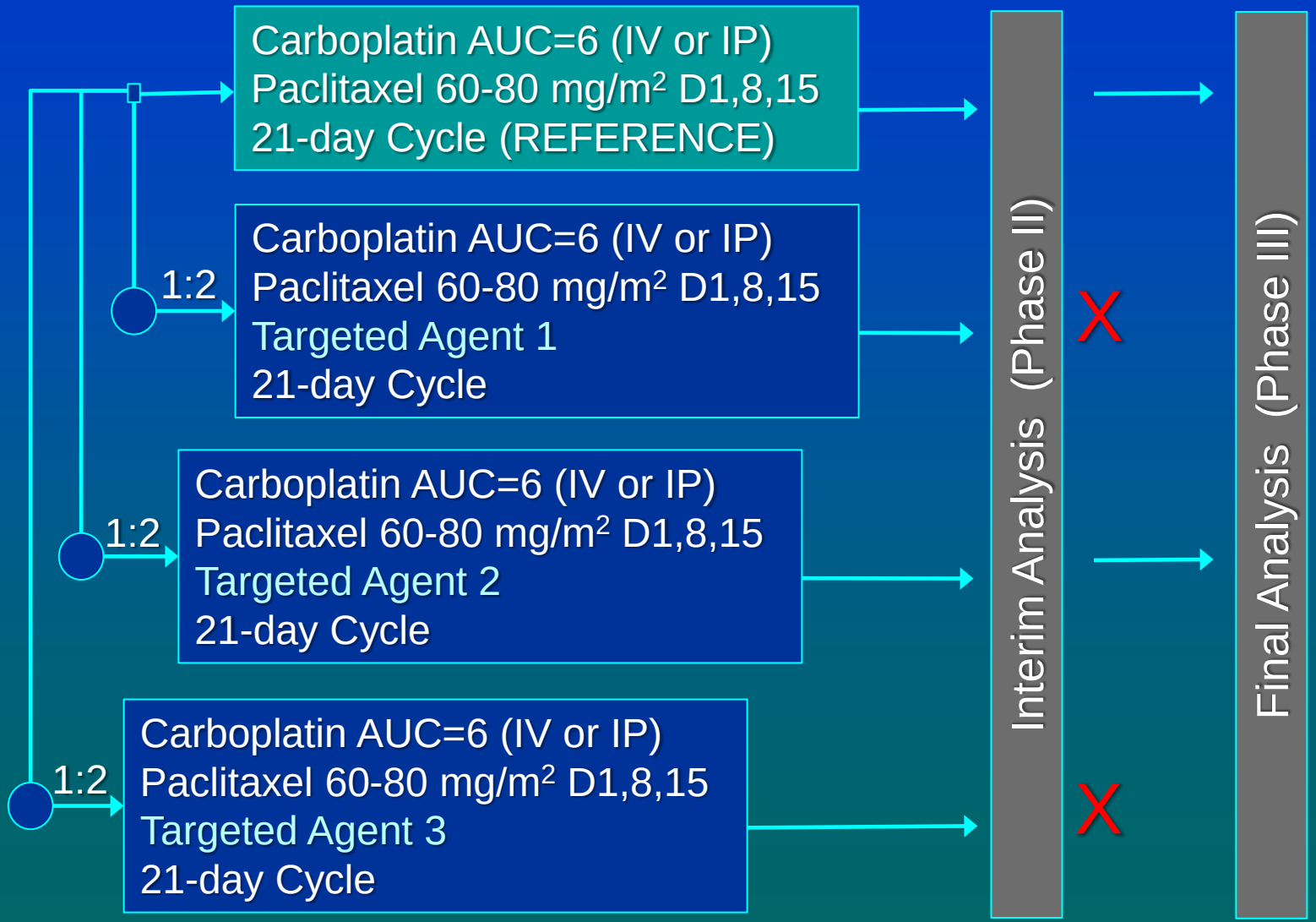
Collaborative development in progress with AbbVie (M13-694) including international participation, seeking EMA and FDA regulatory approval

Open: JAN 2014 (target)
Closed:
Target Accrual: ~1100 pts (264 BRCA1/2 +)

Bell-Mcguinn K, et al. for GOG

Sequential-Selective Trial Design

NACT x3 cycles with interval cytoreduction and tumor specimen acquisition



Targeting HGSC: *The Coming Decade*

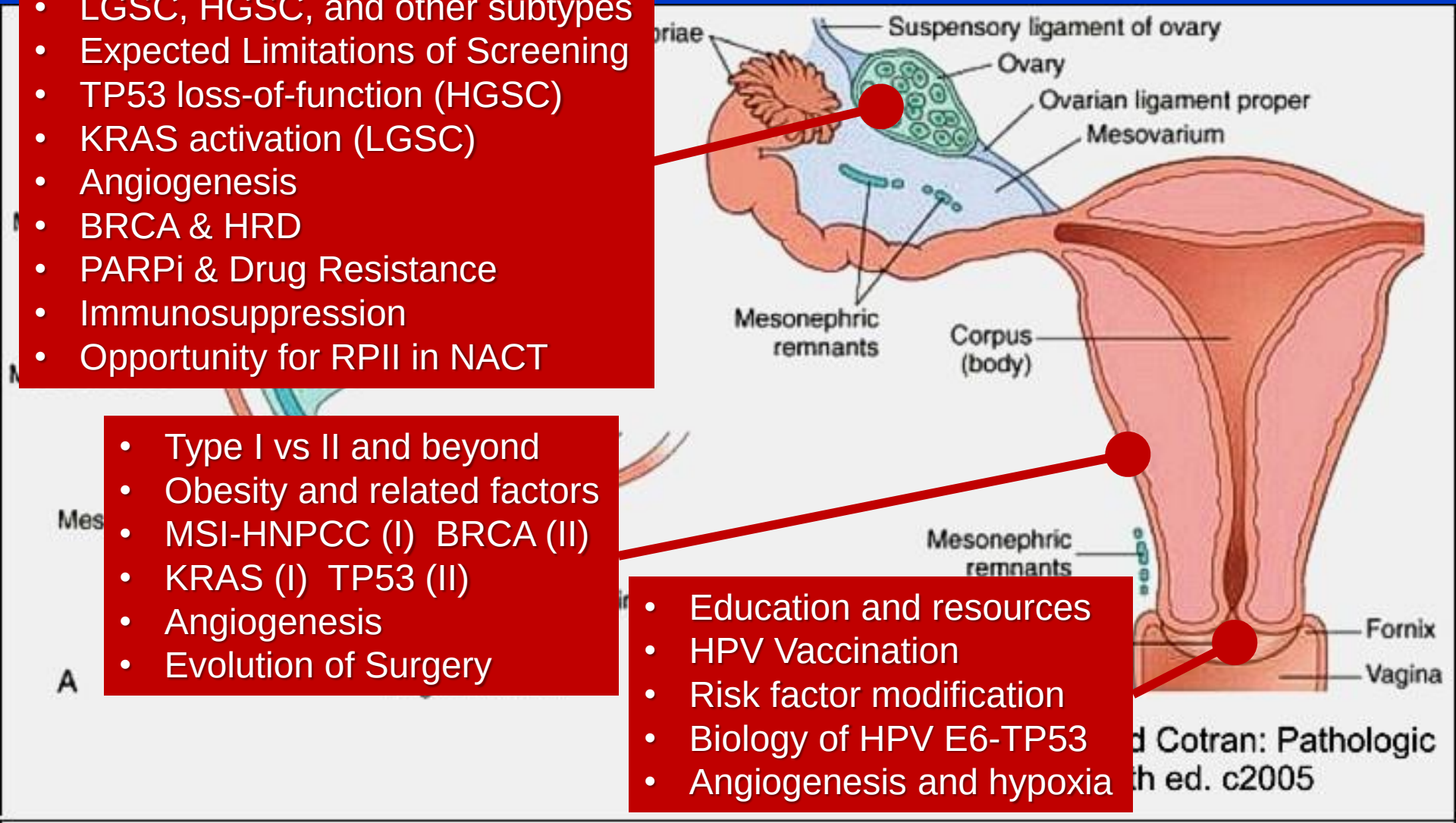
- Targeting angiogenesis, PARP, and the immune response will contribute to improved patient outcomes, but impact on mortality uncertain
- Vaccines are unlikely to be effective without a parallel strategy to modulate immunosuppression

See Webcast Discussion: Elizabeth Eisenhauer (Developmental Therapeutics 27-SEP) Combinations of Targeted Agents

- Exploitation of synthetic lethality, particularly in relationship to apoptotic signaling (TP53) and drug resistance remains a high priority
- Restoration of tumor suppressor function, especially TP53, is a molecular engineering challenge with great potential
- Understanding the biology of cancer stem-like populations will drive new treatment paradigms
- Federal research funding is not likely to increase, and will emphasize small randomized trials with targeted agents and predictive biomarkers.

Müllerian Counterpoints

- LGSC, HGSC, and other subtypes
- Expected Limitations of Screening
- TP53 loss-of-function (HGSC)
- KRAS activation (LGSC)
- Angiogenesis
- BRCA & HRD
- PARPi & Drug Resistance
- Immunosuppression
- Opportunity for RPII in NACT



- Type I vs II and beyond
- Obesity and related factors
- MSI-HNPCC (I) BRCA (II)
- KRAS (I) TP53 (II)
- Angiogenesis
- Evolution of Surgery

- Education and resources
- HPV Vaccination
- Risk factor modification
- Biology of HPV E6-TP53
- Angiogenesis and hypoxia