GASCO 2014

Best of ASCO 2014 Gynecologic Oncology

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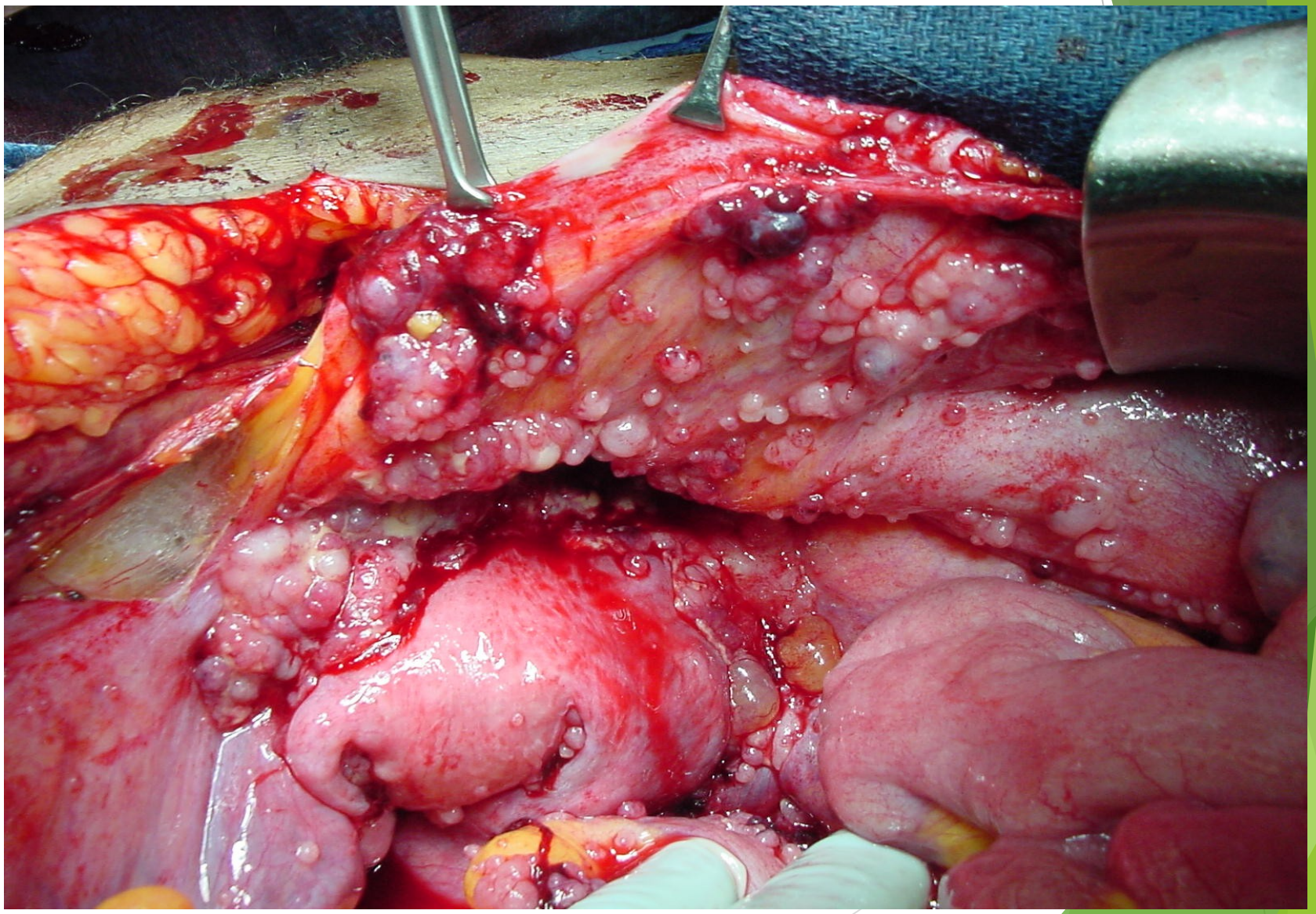
Presented by:

GRU CANCER CENTER
GEORGIA REGENTS UNIVERSITY

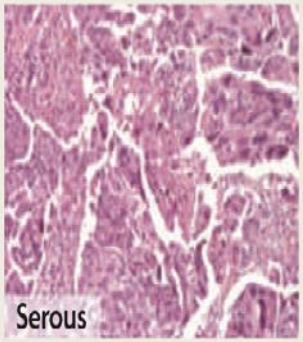
Ovarian Cancer

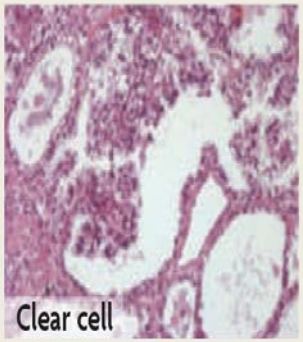
- 200,000 new cases world wide
- 2nd most common gynecologic malignancy
- Leading cause of gynecologic cancer related death in Europe and the US,
- 1 in 70 women in US will develop ovarian cancer, 1 in 100 will die of it
- 75% of cases are diagnosed at advanced stage, making this a lethal cancer
- Like breast cancer, 8-10% of ovarian cancer is hereditary

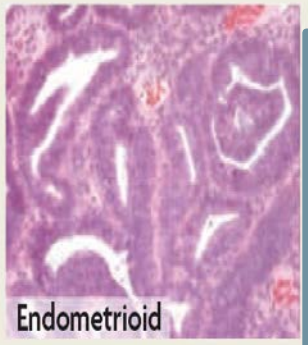
Newly Diagnosed Advanced Ovarian Cancer



Coleman RL, Monk BJ, Sood AK, Herzog TJ. Nat Rev Clin Oncol. 2013 Apr;10(4):211-24.







"OVARIAN CANCER IS ERROUNESLY REGARDED AS A SINGLE DISEASE"

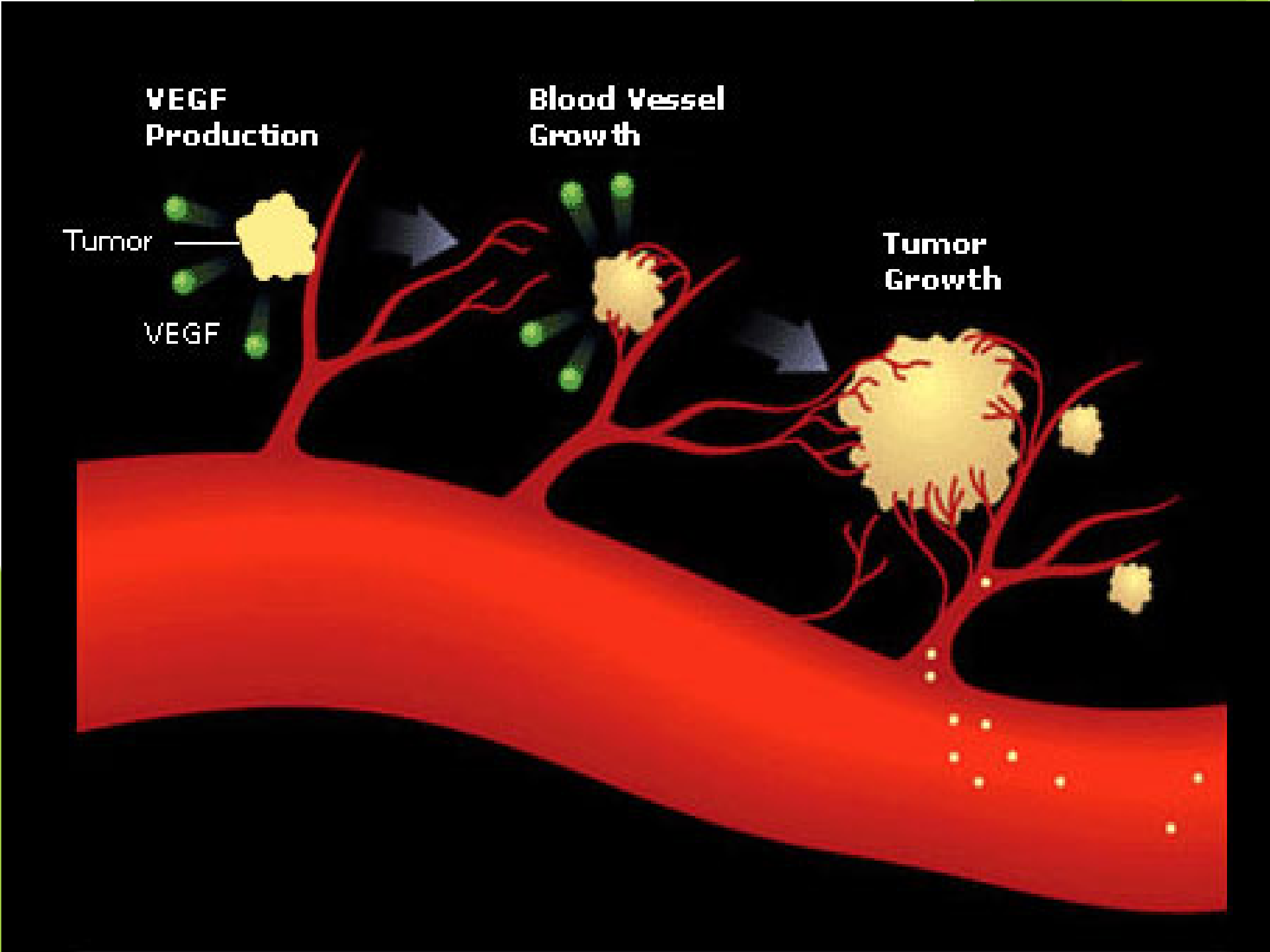
DUALISTIC MODEL OF OVARIAN CANCER

Type	Histology	Precursor	Molecular features
I	Low-grade serous carcinoma	Cystadenoma–borderline tumour–carcinoma sequence	Mutations in *KRAS* and/or *BRAF* (≥60%)
I	Low-grade endometrioid carcinoma	Endometriosis and endometrial cell-like hyperplasia*	Mutations in *CTNNB1*, *PTEN* and *PIK3CA* with microsatellite instability
I	Mucinous carcinoma	Cystadenoma–borderline tumour–carcinoma sequence; metastases from bowel	Mutations in *KRAS*; *TP53* mutation associated with transition from borderline tumour to carcinoma
I	Clear cell carcinoma	Endometriosis	*PTEN* mutation or loss of heterozygosity; *PIK3CA* mutation‡
II	High-grade serous carcinoma	*De novo* in epithelial inclusion cysts; fallopian tube	*TP53* mutation (up to 80%) and *BRCA1* dysfunction
II	High-grade endometrioid carcinoma	Epithelial inclusion glands or cysts	*TP53* mutation and *BRCA1* dysfunction; *PIK3CA* mutation

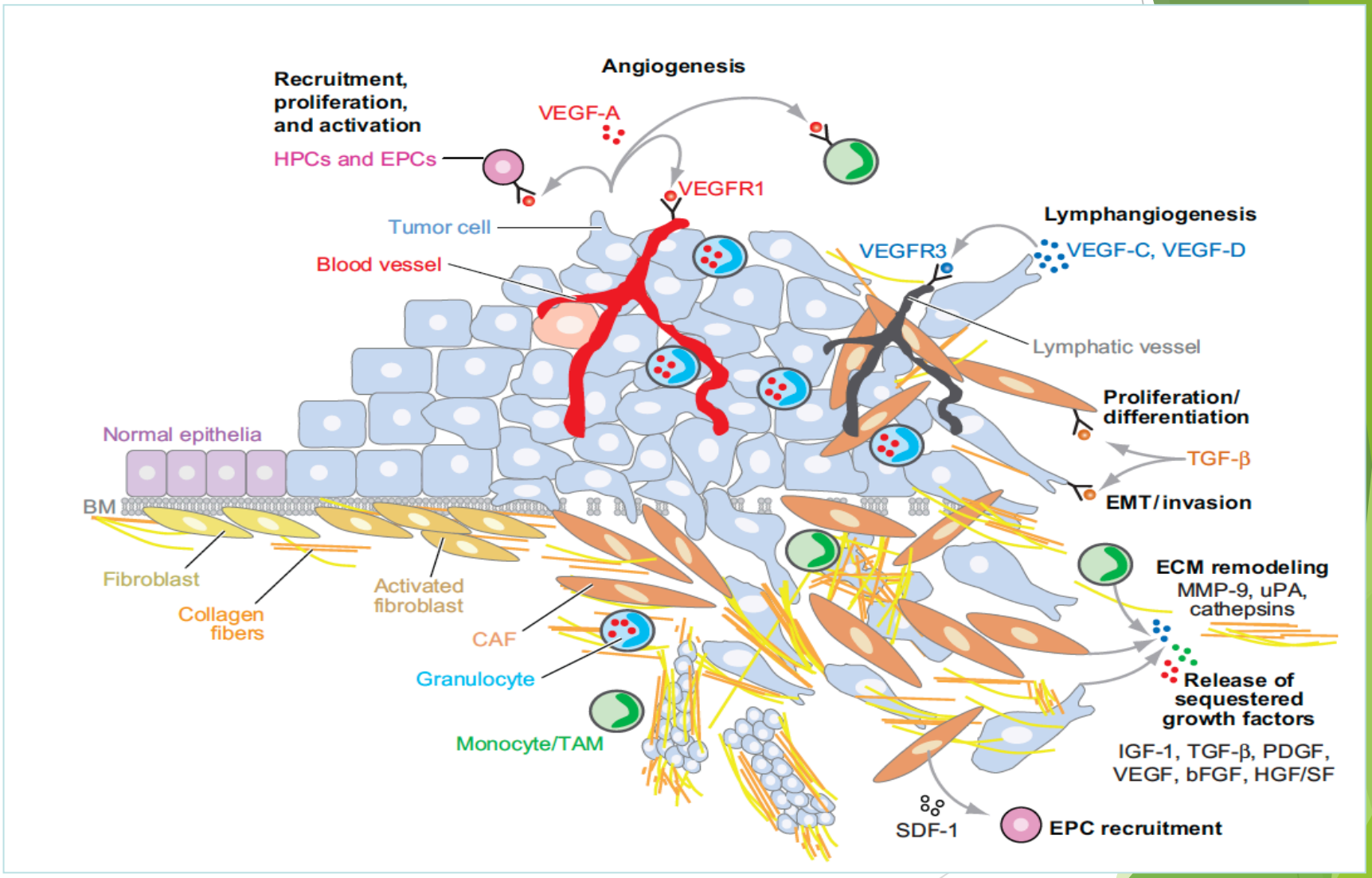
Bast RC Nature Reviews; Vol 9; June 2009

High grade serous ovarian cancer

- Usually presents with advanced disease
- Characterised by genomic instability and molecular heterogeneity
- Antiangiogenic agents and PARP inhibitors have demonstrated significant efficacy


VEGF
Production
Blood Vessel
Growth
Tumor
VEGF
Tumor
Growth

Angiogenesis in Tumor Progression



Bacac et al, 2008.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Bevacizumab in Ovarian Cancer

Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D., Sharadah Essapen, M.D., Charlie Gourley, M.D., Alain Lortholary, M.D., Frédéric Selle, M.D., Mansoor R. Mirza, M.D., Arto Leminen, M.D., Marie Plante, M.D., Dan Stark, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D., and Amit M. Oza, M.D., for the ICON7 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

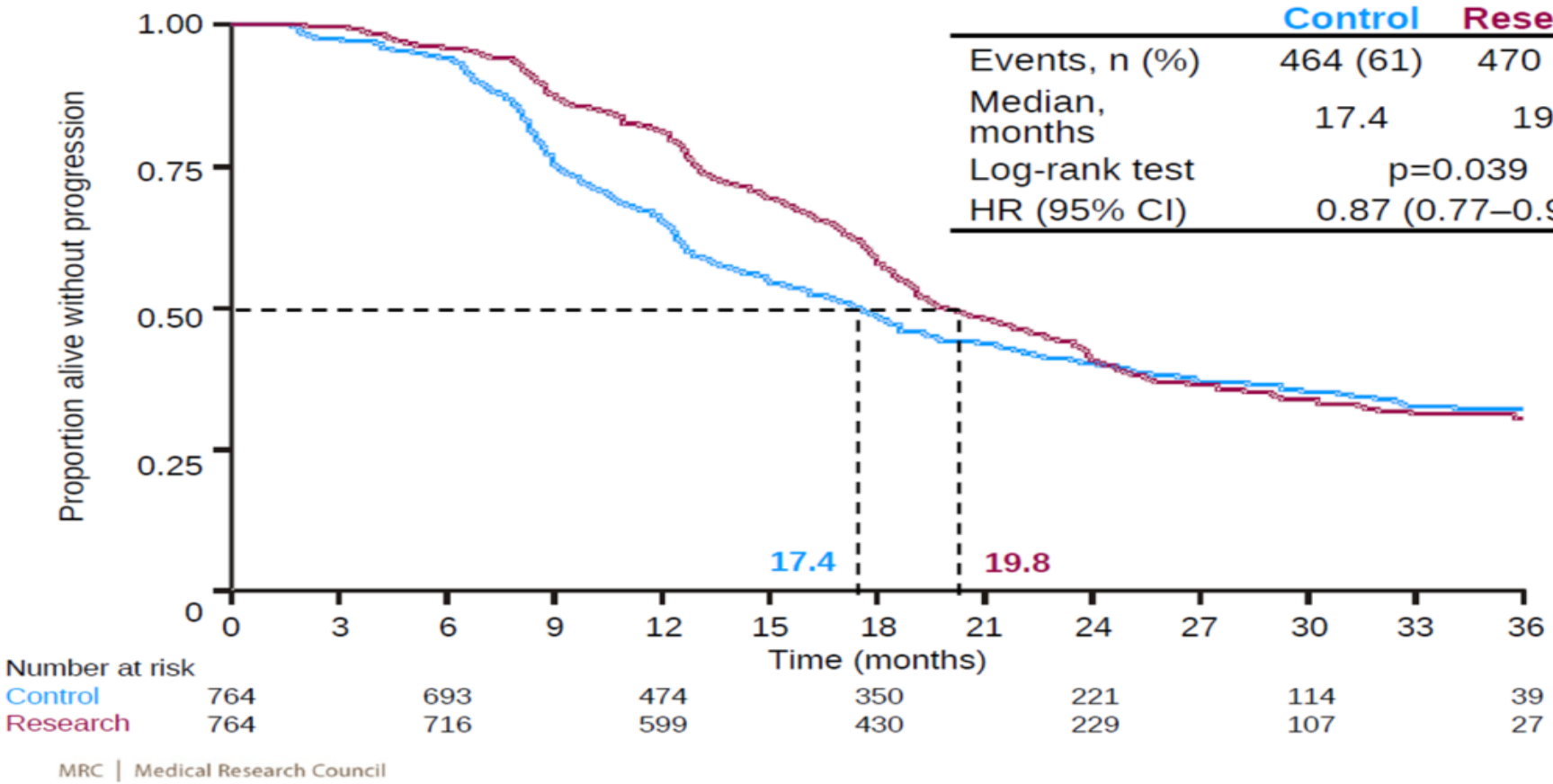
Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*

ICON7
Bevacizumab in Ovarian Cancer

Updated PFS

MRC Clinical Trials Unit

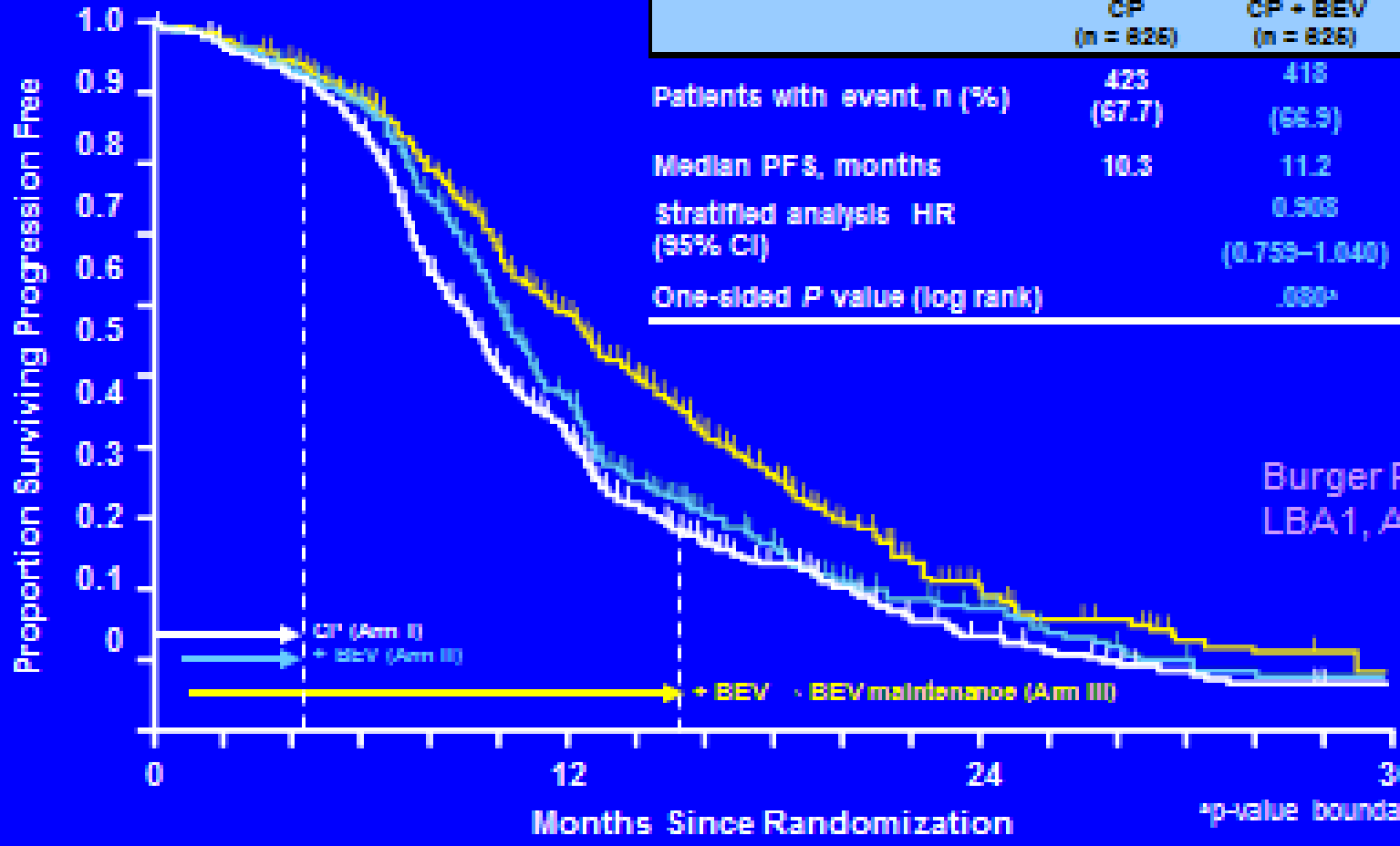


MRC | Medical Research Council

- European Medicines Agency (EMA) granted bevacizumab a license for first line treatment of stage IIIB, IIIC and IV ovarian cancer in 2011

GOG-0218: Investigator-Assessed PFS

	Arm I CP (n = 826)	Arm II CP + BEV (n = 826)	Arm III CP + BEV → BEV (n = 823)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided *P* value (log rank)		.080*	<.0001*



Burger RA et al.
LBA1, ASCO 2010

Bevacizumab currently not licensed for the treatment of ovarian cancer in the US

Abstract 5502: Molecular subgroup of high-grade serous ovarian cancer (HGSOC) as a predictor of outcome following bevacizumab

Charlie Gourley,[1] Andrena McCavigan,[2] Timothy Perren,[3] James Paul,[4] Caroline Ogilvie Michie,[5] Michael Churchman,[1] Alistair Williams,[6] W. Glenn McCluggage,[7] Mahesh Parmar,[8] Richard S. Kaplan,[8] Laura A. Hill,[2] Iris A Halfpenny,[2] Eamonn J. O'Brien,[2] Claide Raji,[2] Steve Deharo,[2] Timothy Davison,[2] Patrick Johnston,[9] Katherine E. Keating,[2] D. Paul Harkin,[2,9] Richard D. Kennedy[2,9]

[1]University of Edinburgh Cancer Research UK Centre, MRC IGMM, Edinburgh, UK

[2]Almac Diagnostics, 19 Seagoe Industrial Estate, Craigavon, UK

[3]St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK

[4]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK

[5]Ninewells Hospital, Dundee, UK

[6]Division of Pathology, University of Edinburgh, Edinburgh, UK

[7]Department of Pathology, Royal Group of Hospitals Trust, Belfast, UK

[8]MRC Clinical Trials Unit, London, UK

[9]Center for Cancer Research and Cell Biology, Queen's University of Belfast, UK

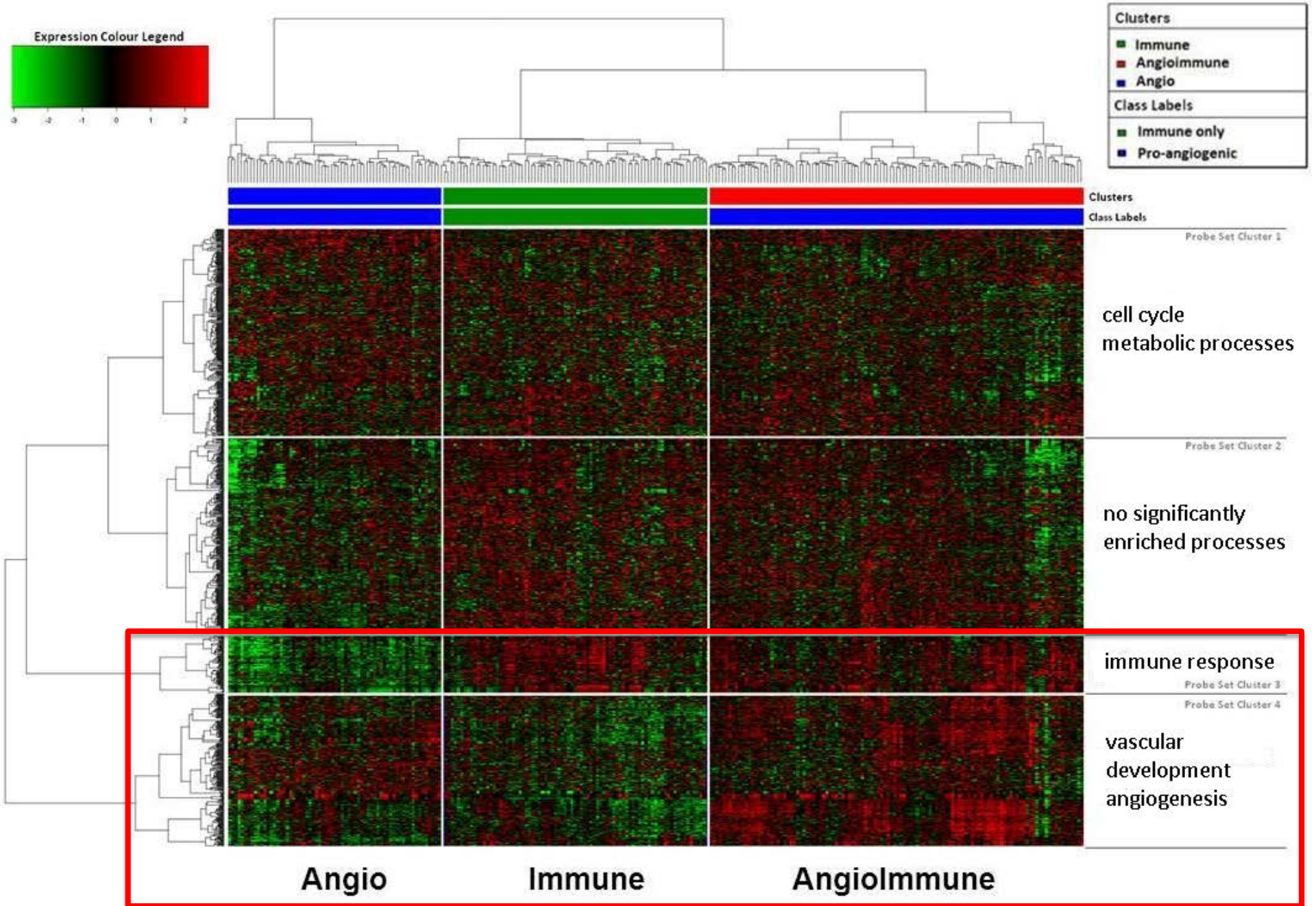
Study aim

Identify molecular subtypes of high grade serous ovarian cancer in order to facilitate individualisation of care

Edinburgh patients: case identification

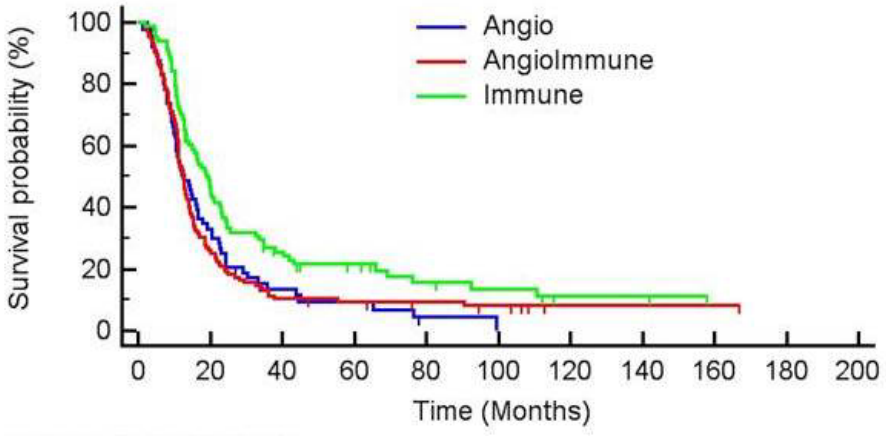
- 387 primary treatment naïve FFPE specimens
- Platinum-based first line chemotherapy
- 30 specimens failed quality control
- 92 non high grade serous
- **265 high grade serous**

Edinburgh dataset; unsupervised hierarchical clustering



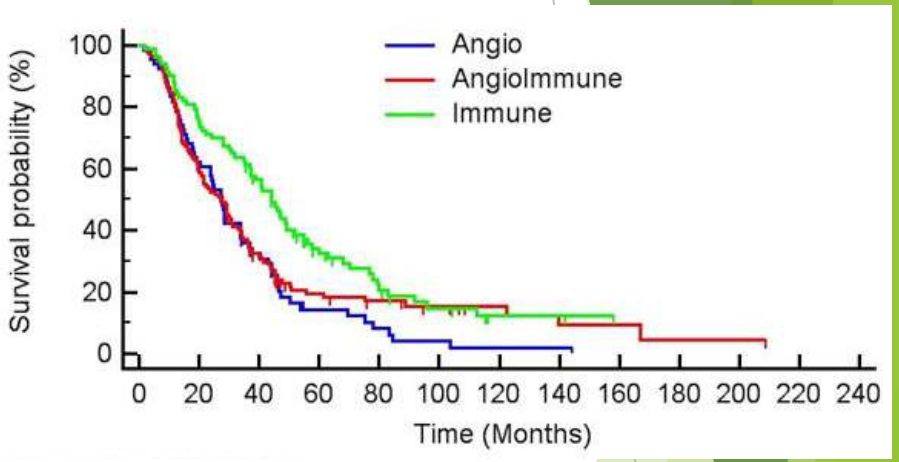
Edinburgh dataset; survival analysis

Progression free survival



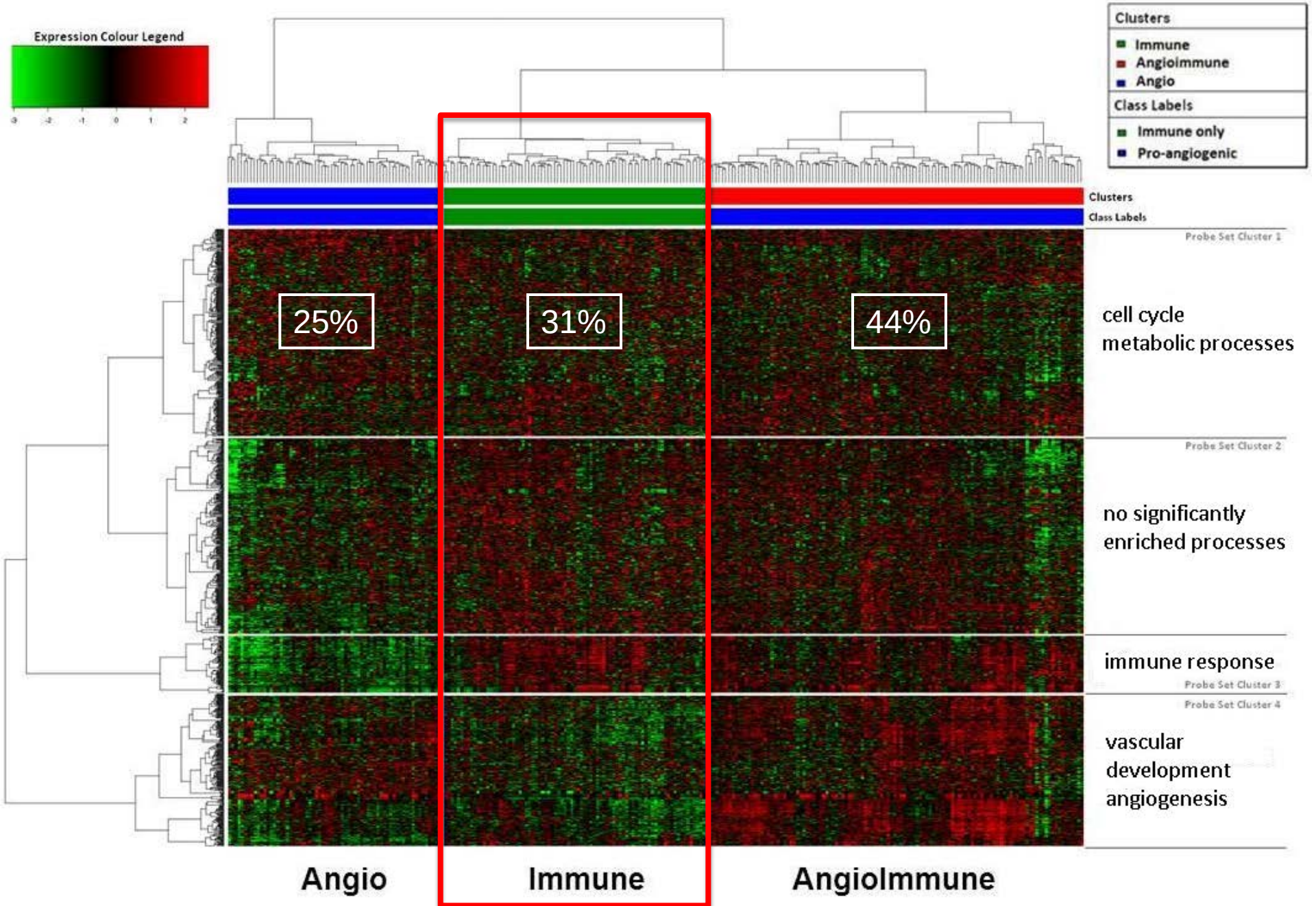
	HR	95% C.I.	p-value
Immune vs Angioimmune	0.60	0.44-0.82	0.002
Immune vs Angio	0.64	0.45-0.92	0.02

Overall survival

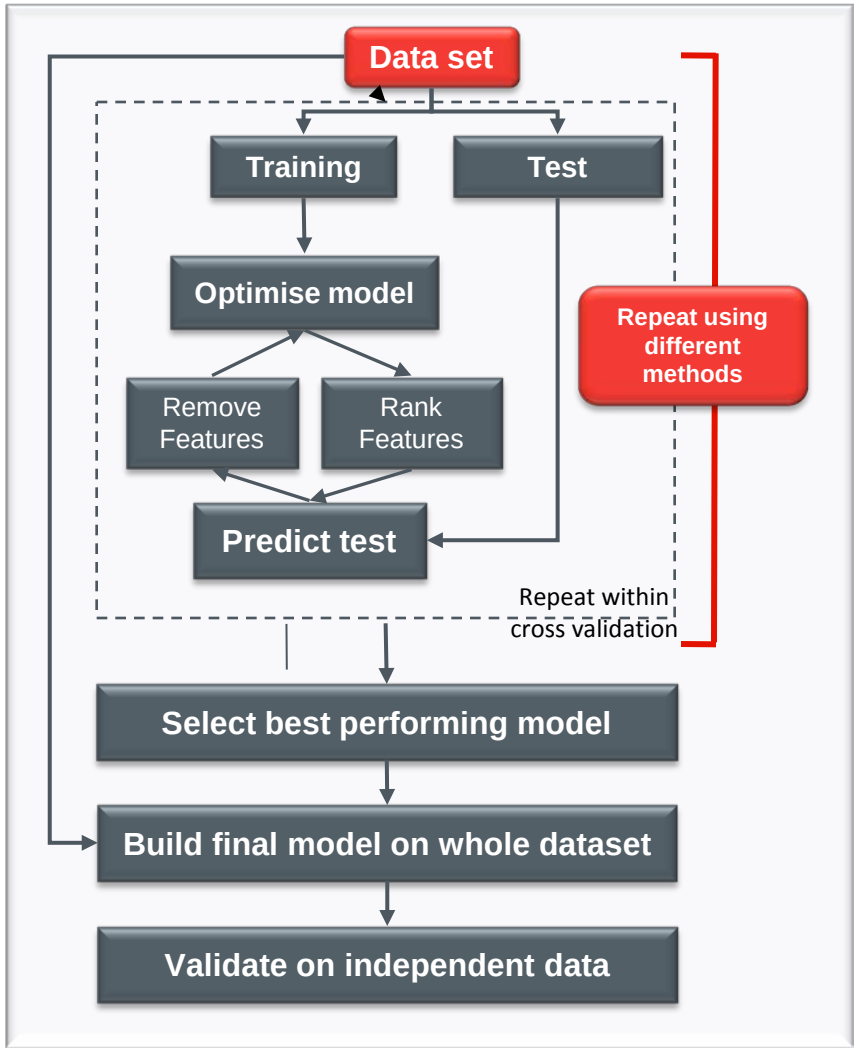


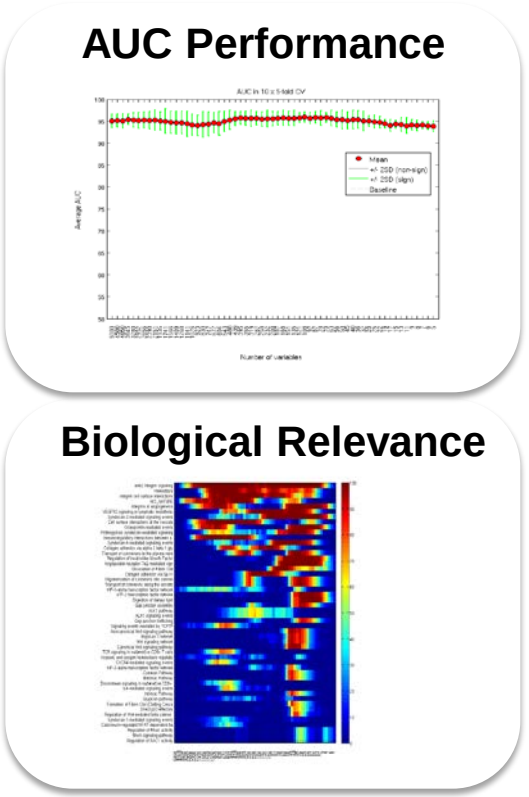
	HR	95% C.I.	p-value
Immune vs Angioimmune	0.58	0.41-0.82	0.001
Immune vs Angio	0.55	0.37-0.80	0.001

Edinburgh dataset; unsupervised hierarchical clustering



Edinburgh dataset; Immune subgroup signature generation





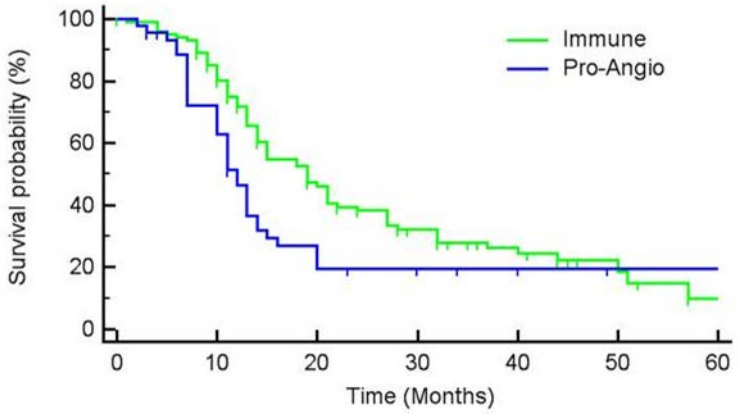
63-gene signature developed to distinguish Immune subgroup patients from those in the Angio and Angioimmune subgroups.

Application of the 63-gene Immune signature to the Tothill dataset *in silico*

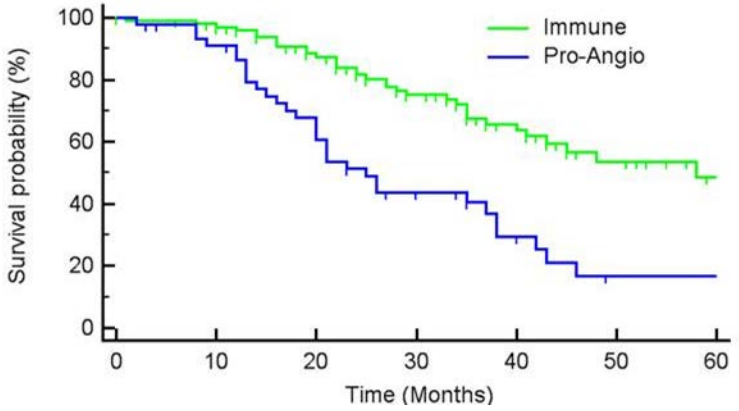
- 285 fresh frozen ovarian cancers
- 152 high grade serous
- Paclitaxel and carboplatin chemotherapy
- Profiled on Affymetrix U133A Plus 2 platform

Application of signature to Tothill dataset

PFS



OS



Univariate: **HR = 0.661 [0.439-0.996], p = 0.048** **HR = 0.357 [0.219-0.582], p<0.001**

Multivariable: **HR = 0.645 [0.423-0.982], p = 0.041** **HR = 0.343 [0.206-0.571], p<0.001**

Application of the 63-gene Immune signature to the ICON7 translational specimens

- The immune molecular subtype is characterised by absence of angiogenic biology
- We hypothesized that this group would not benefit from anti-angiogenic agents
- The Immune assay was therefore applied to translational research samples from the ICON7 study (carboplatin and paclitaxel +/- bevacizumab)
- 88% power to detect interaction >2 in the predicted direction for PFS (α=0.1, one-tail)

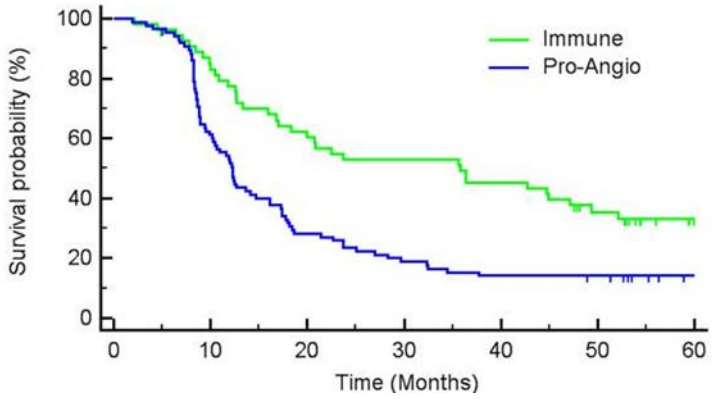
ICON7 translational research patients: case identification

- ICON7 patients consenting to translational research from UK, France, Canada, Australia, New Zealand, Denmark, Finland, Norway, Sweden and Spain
- 375 primary treatment naïve FFPE specimens
- 8 specimens failed quality control
- 83 non high grade serous
- **284 high grade serous**

Presented by: Charlie Gourley

Immune signature prognostic within the control arm of ICON7

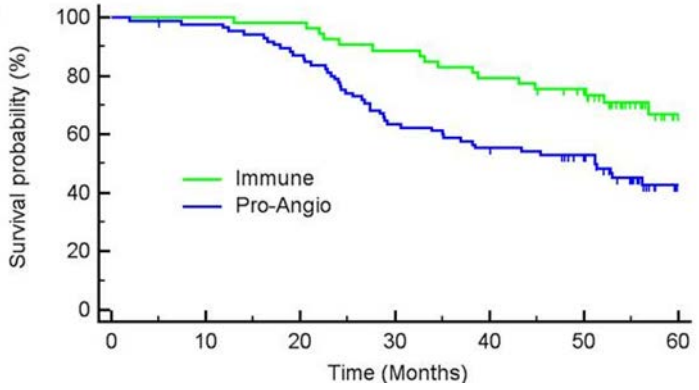
PFS



Univariate: **HR = 0.47 [0.32-0.71], p < 0.001**

Multivariable: **HR = 0.52 [0.33-0.81], p = 0.004**

OS

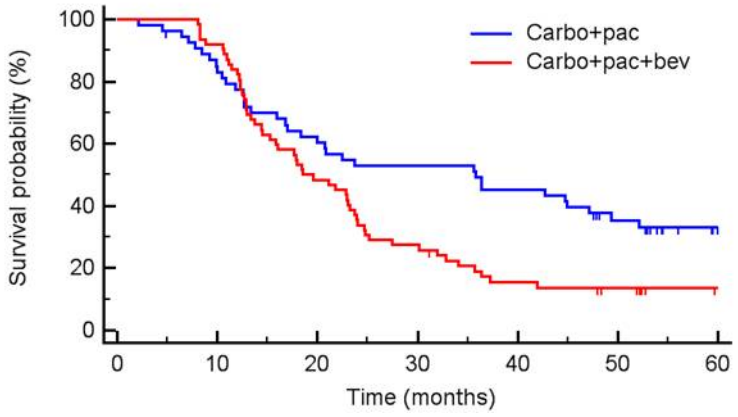


HR = 0.45, [0.26-0.79], p =0.005

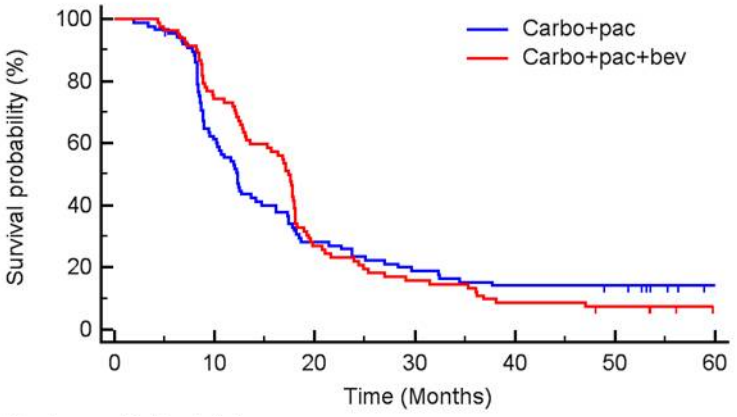
HR = 0.53 [0.29-0.96], p = 0.04

Immune subgroup patients have inferior progression free survival when treated with bevacizumab

Immune subgroup;
41% of ICON7 TR patients



Non-immune (pro-angiogenic) subgroup;
59% of ICON7 TR patients

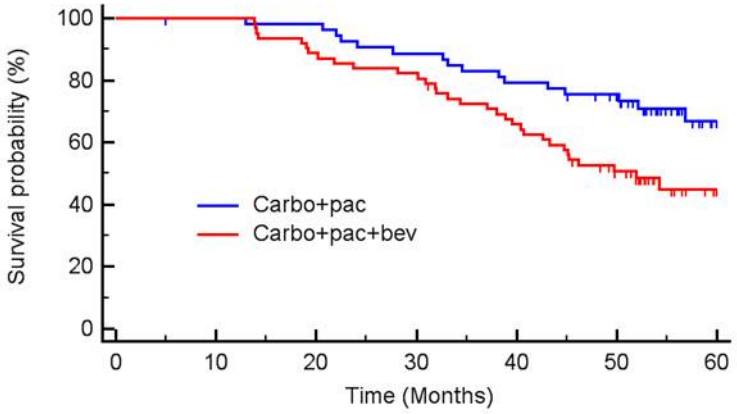


Test for interaction, p=0.015

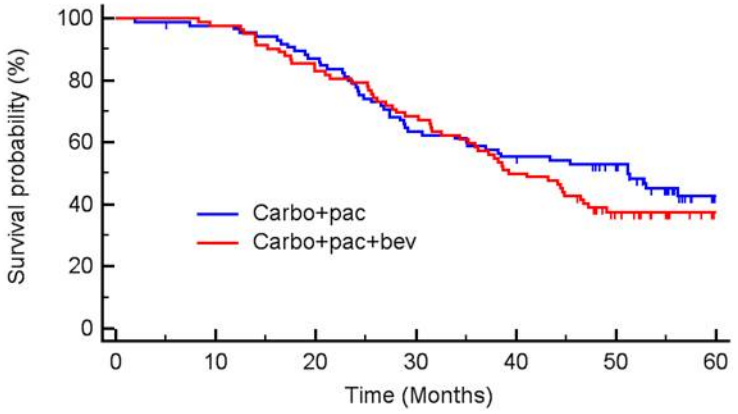
	Immune subgroup	Proangiogenic subgroup
Non-proportionality test	p=0.048	p=0.003
Restricted mean PFS in months (se)	C/P 29.7 (2.2) C/P/Bev 23.8 (1.8)	C/P 18.3 (1.5) C/P/Bev 19.3 (1.3)
Diff in restricted mean PFS (95% ci)	-5.9 (-11.5 to -0.3)	1.0 (-2.9 to 4.9)
Median PFS in months	C/P 35.8 C/P/Bev 18.5	C/P 12.3 C/P/Bev 17.4

Immune subgroup patients have inferior overall survival when treated with bevacizumab

Immune subgroup



Non-immune (pro-angiogenic) subgroup



Test for non-proportionality negative in both molecular subgroups

	Immune subgroup	Proangiogenic subgroup
Univariate	HR 2.00 (1.11-3.61), p=0.022	HR 1.19 (0.80-1.78), p=0.386
	Test for interaction, p=0.075	
Multivariate	HR 2.37 (1.27-4.41), p=0.007	HR 1.10 (0.73-1.66), p=0.637
	Test for interaction, p=0.020	

Discussion

Why might the Immune subgroup be disadvantaged by bevacizumab therapy?

1) Concomitant administration with chemo compromises chemotherapy efficacy?

2) Inhibition of angiogenesis negatively affects tumour cell interaction with the host immune system?

Clinicopathological characteristics of the ICON7 TR patients

		TR patients (375 patients)		Non-TR patients (1153 patients)	
		Control arm (189 patients)	Bevacizumab arm (186 patients)	Control arm (575 patients)	Bevacizumab arm (578 patients)
Median age		57 years		57 years	
FIGO stage	I	16 (8%)	13 (7%)	49 (9%)	41 (7%)
	II	18 (10%)	24 (13%)	62 (11%)	59 (10%)
	III	139 (74%)	127 (68%)	383 (67%)	396 (69%)
	IV	16 (8%)	22 (12%)	81 (14%)	82 (14%)
ECOG performance status	0	74 (39%)	84 (45%)	286 (50%)	251 (43%)
	1	98 (52%)	92 (49%)	256 (45%)	274 (47%)
	2	12 (6%)	5 (3%)	29 (5%)	40 (7%)
	unknown	5 (3%)	5 (3%)	4 (1%)	13 (2%)
Histology*	serous	131 (69%)	132 (71%)	415 (72%)	415 (72%)
	non-serous	58 (31%)	54 (29%)	160 (28%)	163 (28%)
Debulking	0	71 (38%)	65 (35%)	282 (49%)	275 (48%)
	0-1cm	39 (21%)	49 (26%)	136 (24%)	145 (25%)
	>1cm	63 (33%)	57 (31%)	136 (24%)	139 (24%)
	no surgery	4 (2%)	1 (1%)	13 (2%)	12 (2%)
	unknown	12 (6%)	14 (8%)	8 (1%)	7 (1%)

*pat patients)

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	unknown	12 (6%)	14 (8%)	8 (1%)	7 (1%)

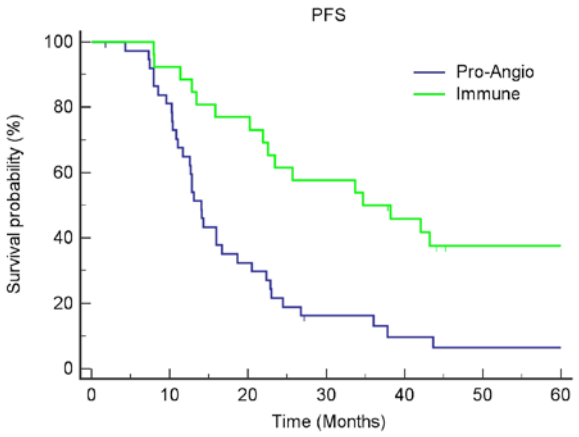
*pat patients)

Immune subgroup patients only have improved outcome if they get good surgery

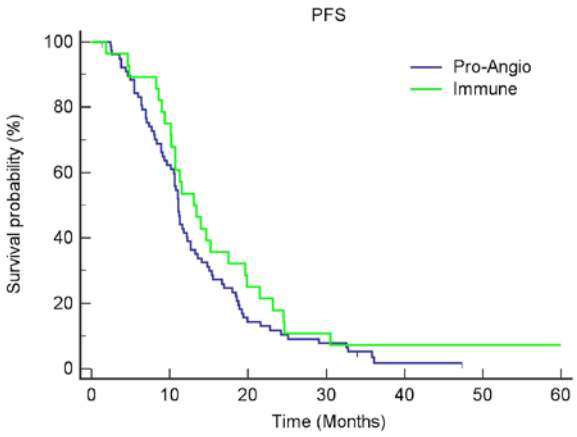
Optimal surgery

Suboptimal surgery

Edinburgh patients

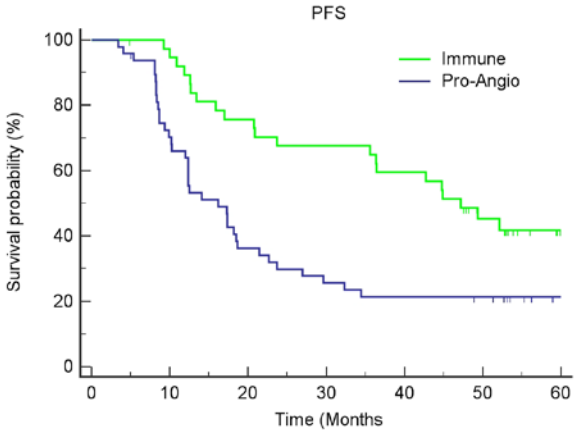


HR=0.34, p<0.001

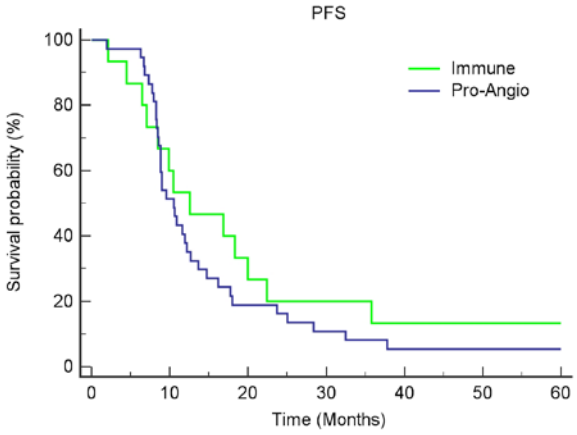


HR=0.71, p=0.13

ICON7 patients

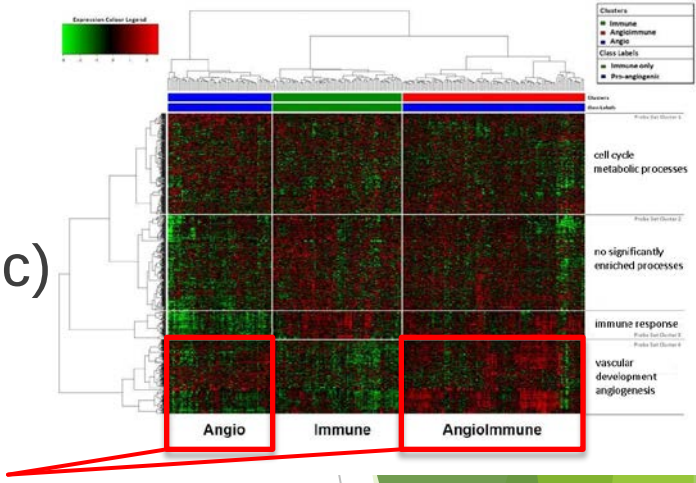


HR=0.44, p=0.003



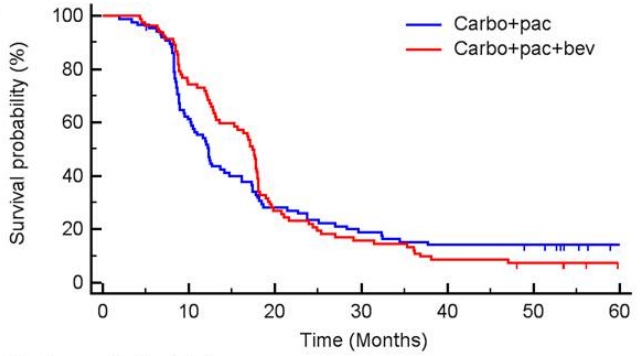
HR=0.64, p=0.12

Discussion



What about the non-Immune (pro-angiogenic) subgroup of patients?

- High expression of genes involved in angiogenesis/vascular development
- Trend towards improved PFS following addition of bevacizumab in this analysis (median 17.4 versus 12.3 months)
- Clear evidence of curve crossing with maximal benefit at point when therapy sto
- Issue of duration of therapy should be addressed by AGO-OVAR 17 study (15 vs 30 months bevacizumab)



Presented by: Charlie Gourley

Conclusions

- Unsupervised analysis identifies a subgroup of high grade serous ovarian cancer with superior survival
- Significant biology underlies this classification
- The Immune signature was prognostic in two further datasets
- The Immune signature identifies patients whose outcome appears to be adversely affected by the addition of bevacizumab
- There is a trend towards an improved outcome with the addition of bevacizumab outside of this subgroup
- This is the first assay to convincingly predict sensitivity to antiangiogenic therapy in any cancer
- These findings require urgent further validation within other bevacizumab treated trial populations

JGOG3017/GCIG TRIAL

Randomized Phase III Trial of Paclitaxel plus Carboplatin (TC) Therapy versus Irinotecan plus Cisplatin (CPT-P) Therapy as First Line Chemotherapy for Clear Cell Carcinoma of the Ovary

Aikou Okamoto[*1], Toru Sugiyama[*2], Tetsutaro Hamano[*3], Jae-Weon Kim[*4], Byoung-Gie Kim[*5], Takayuki Enomoto[*6], Daisuke Aoki[*7], Yasuhisa Terao[*8], Nao Suzuki[*9], Mikio Mikami[*10], Nobuo Yaegashi[*11], Kiyoko Kato[*12], Hiroyuki Yoshikawa[*13], Sandro Pignata[*14], Jerome Alexandre[*15], John Green[*16], Seiji Isonishi[*1], Fumitoshi Terauchi[*17], Keiichi Fujiwara[*18], Kazunori Ochiai[*1]

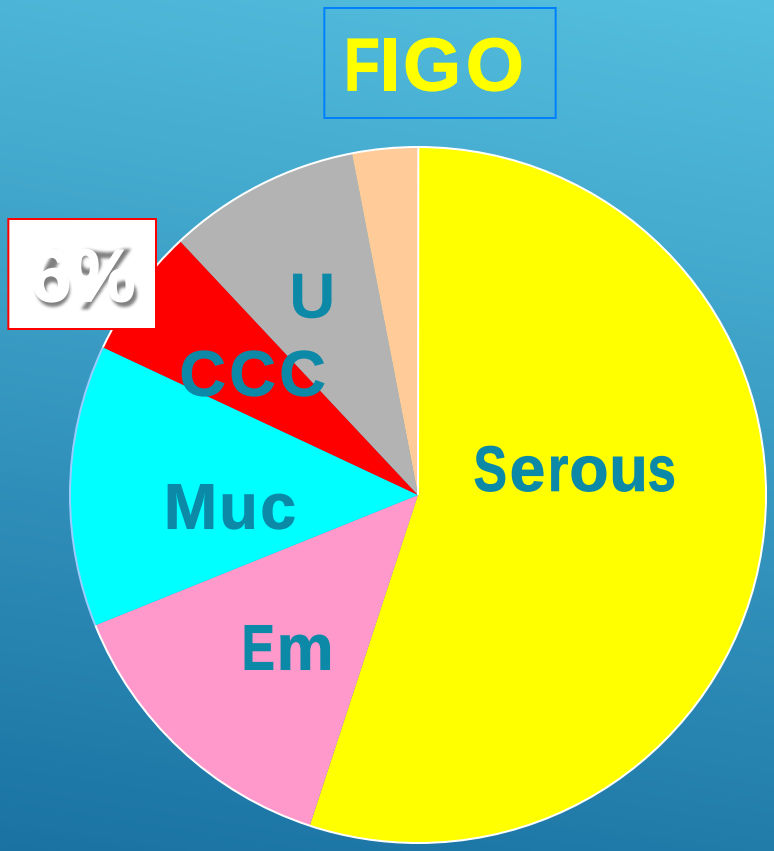
[*1]Jikei University, [*2]Iwate Medical University, [*3] H-STAT, [*4]Seoul National University, [*5]Sungkyunkwan University, [*6]Niigata University, [*7]Keio University, [*8]Juntendo University, [*9]St.Marianna University, [*10]Tokai University, [*11]Tohoku University, [*12]Kyushu University, [*13]University of Tsukuba, [*14]Istituto Nazionale Tumori di Napoli, [*15]Hopital Hotel Dieu, [*16]University of Liverpool, [*17]Tokyo Medical University, [*18]Saitama Medical University International Medical Center

WHAT IS CCC AND WHY IS JAPAN LEADING THE TRIAL?

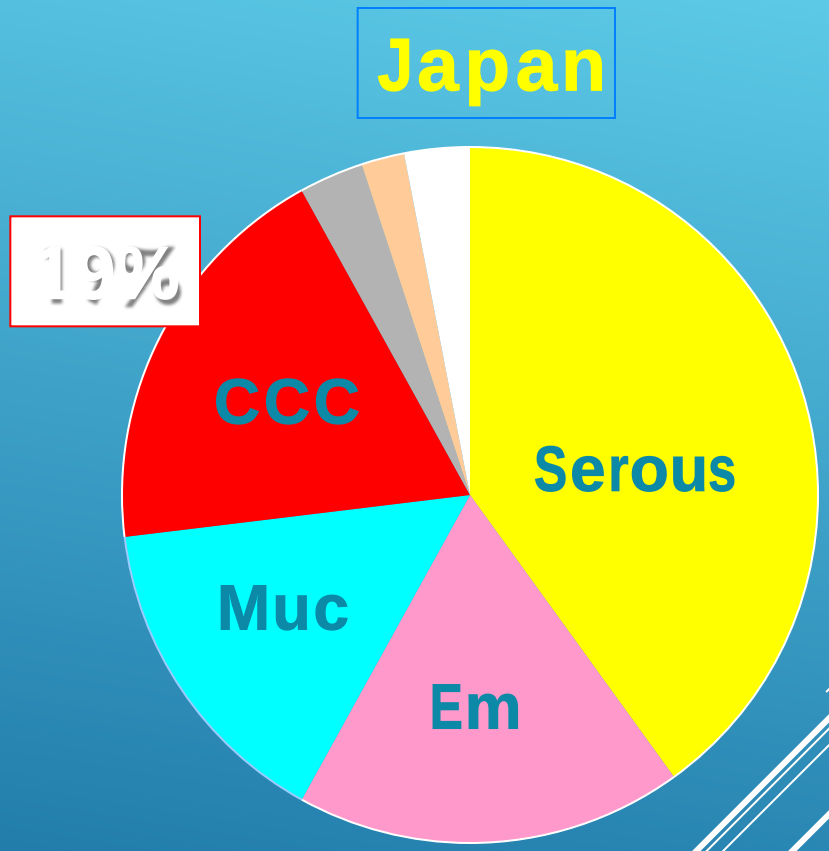
- Clear Cell Carcinoma of the Ovary (CCC) is one of the histological entities of epithelial ovarian cancer (1973, WHO classification)
- Incidence of CCC is rare in Western Countries (5%), but it is not rare in Japan (>20%)
- Retrospective studies conducted in Japan indicated that CCC is less sensitive to chemotherapy and prognosis is poorer than in cases of serous/endometrioid adenocarcinoma of the ovary.

The critical question is whether paclitaxel/carboplatin (TC) therapy, the current standard for epithelial ovarian cancer (EOC) based upon the results of multiple RCTs, is an optimal regimen for CCC. Although the response rate of TC therapy for EOC is approximately 75%, this rate may not be applicable to CCC.

OVARIAN CARCINOMA: HISTOL

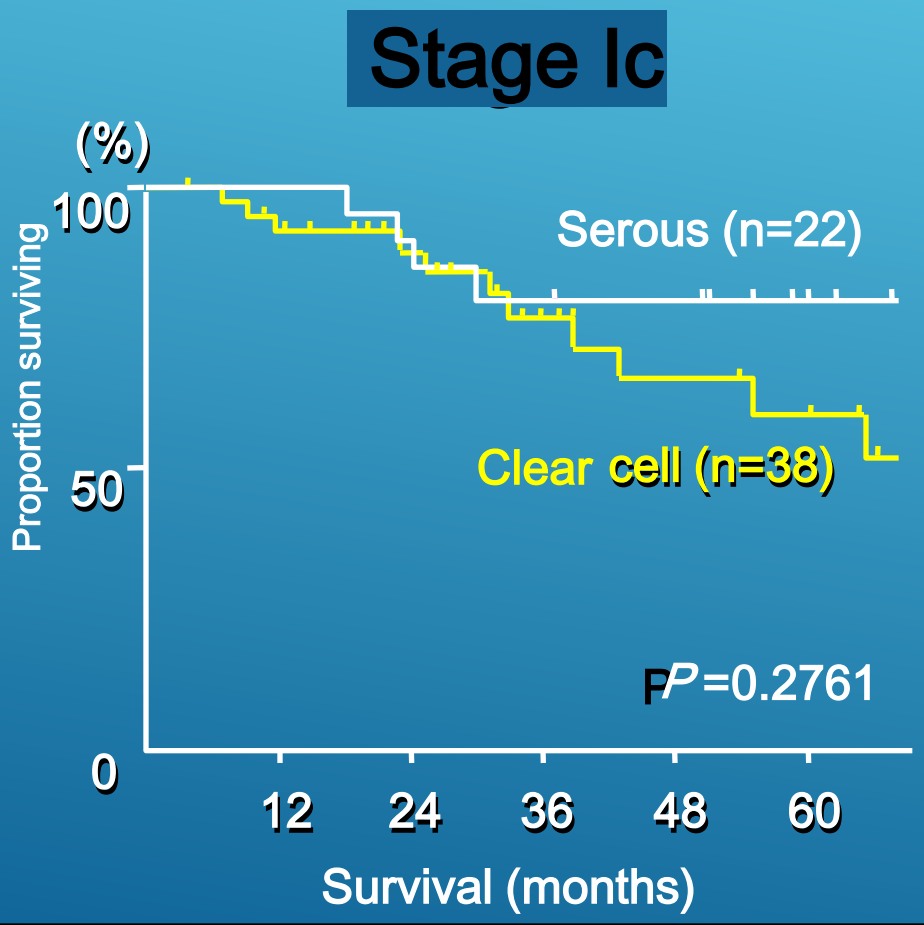


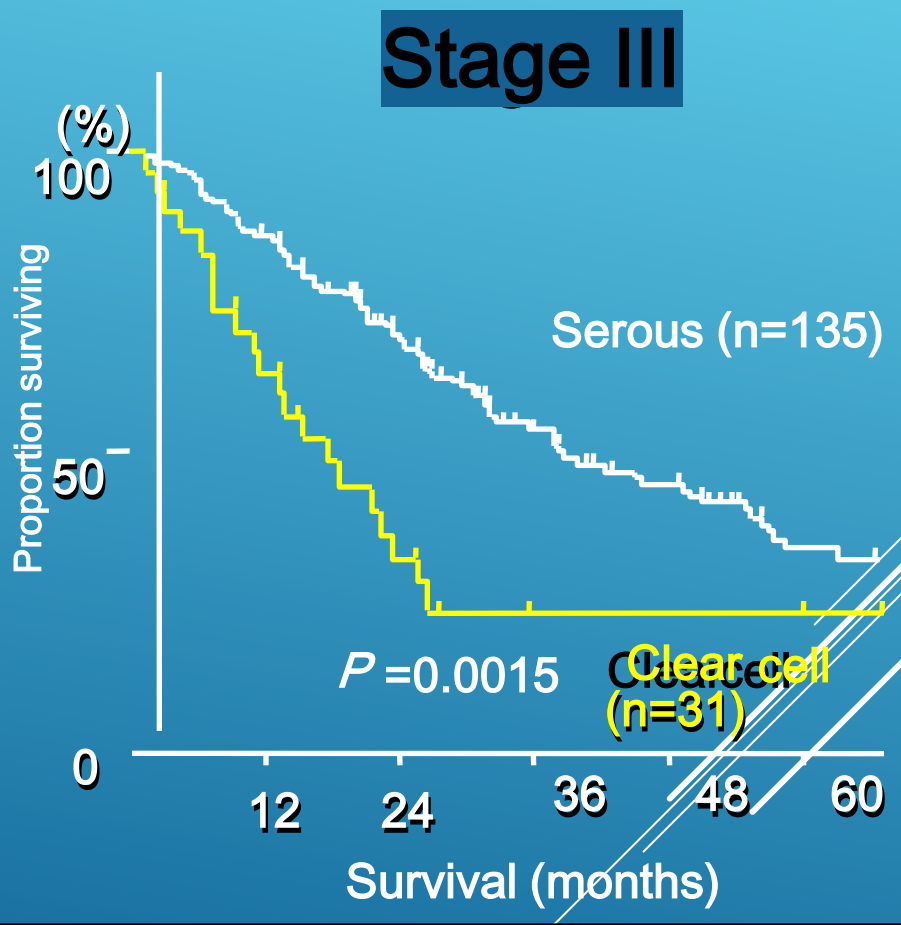
Annual Report 2003



From 562 Hospitals
AOGJ 54:746, 2002

LEAR CELL CARCINOMA VS SEROUS ADENOCARCINOI
OVERALL SURVIVAL





Sugiyama T, et al. *Cancer* 2000; 88:2584-2589

RATIONAL

Retrospective studies[1, 2] and a randomized phase II trial[3] showed that irinotecan is a promising candidate for the treatment of CCC.

1. Takano et al. Oncol Rep. 2006;16(6):1301-6.
2. Takano et al. Int J Clin Oncol. 2007 12(4):256-60
3. Takakura et al. Int J Gynecol Cancer. 2010 ;20:240-7.

JGOG 3017/GCIG: Schema

-Clear Cell Ca
-Stage I~IV

Web RANDOMIZATION

TC
Paclitaxel 175 mg/m^2 (d1)
Carboplatin AUC 6 (d1)
Every 3 wk x 6

CPT-11/CDDP
CPT-11 60 mg/m^2 (d1, 8, 15)
Cisplatin 60 mg/m^2 (d1)
Every 4 wk x 6

326 patients in each arm, 652 total for 4.25 years

Study Chair Toru Sugiyama, MD (Iwate Medical University)
Study Co-Chair Seiji Isonishi, MD (Jikei University School of Medicine)
Fumitoshi Terauchi, MD (Toho University)

JGOG 3017/GCIG: Objectives

- Primary endpoint was progression-free survival (PFS).
- Secondary endpoints were overall survival (OS), response rate (in cases with measurable disease only), and adverse event (frequency and grade).

JGOG 3017/GCIC: Statistical Considerations

- **Sample size calculation**
  - Assuming that the 5 year PFS of TC arm and CPT-P arm are 40% and 50%, respectively, with an accrual period of 4.25 years and total duration of 6.5 years, 652 patients and 323 events are required with a one-sided type I error of 0.05 and a power of 80% using log-rank test.
  - After protocol modification due to an unexpectedly large proportion of patients with non-clear cell carcinoma, with an accrual period of 4.75 years and total duration of 6.75 years, 662 patients are required.

Eligibility

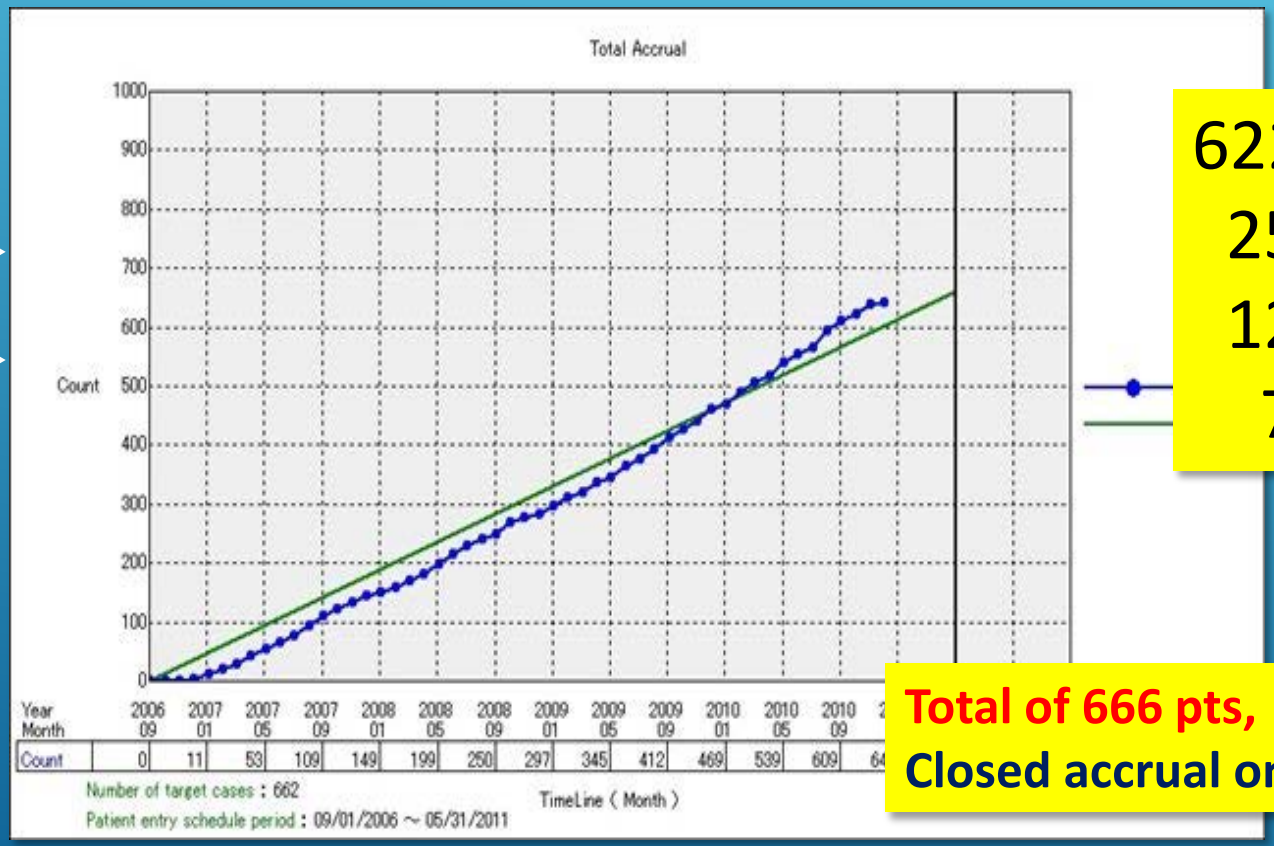
- Stage I to IV CCC

  All patients must have had comprehensive staging surgery for ovarian carcinoma with appropriate tissue available for histological evaluation.

- Patients must be enrolled within 6 weeks after surgery.
- Clear cell histology must be dominant (> 50%).

  The histological diagnosis was confirmed by a international central pathology review (I-CPR) after registration.

GCIG/JGOG 3017: Accrual



622 pts --Japan
25 pts --Korea
12 pts --France
7 pts --UK

Total of 666 pts,
Closed accrual on March 1, 2011.

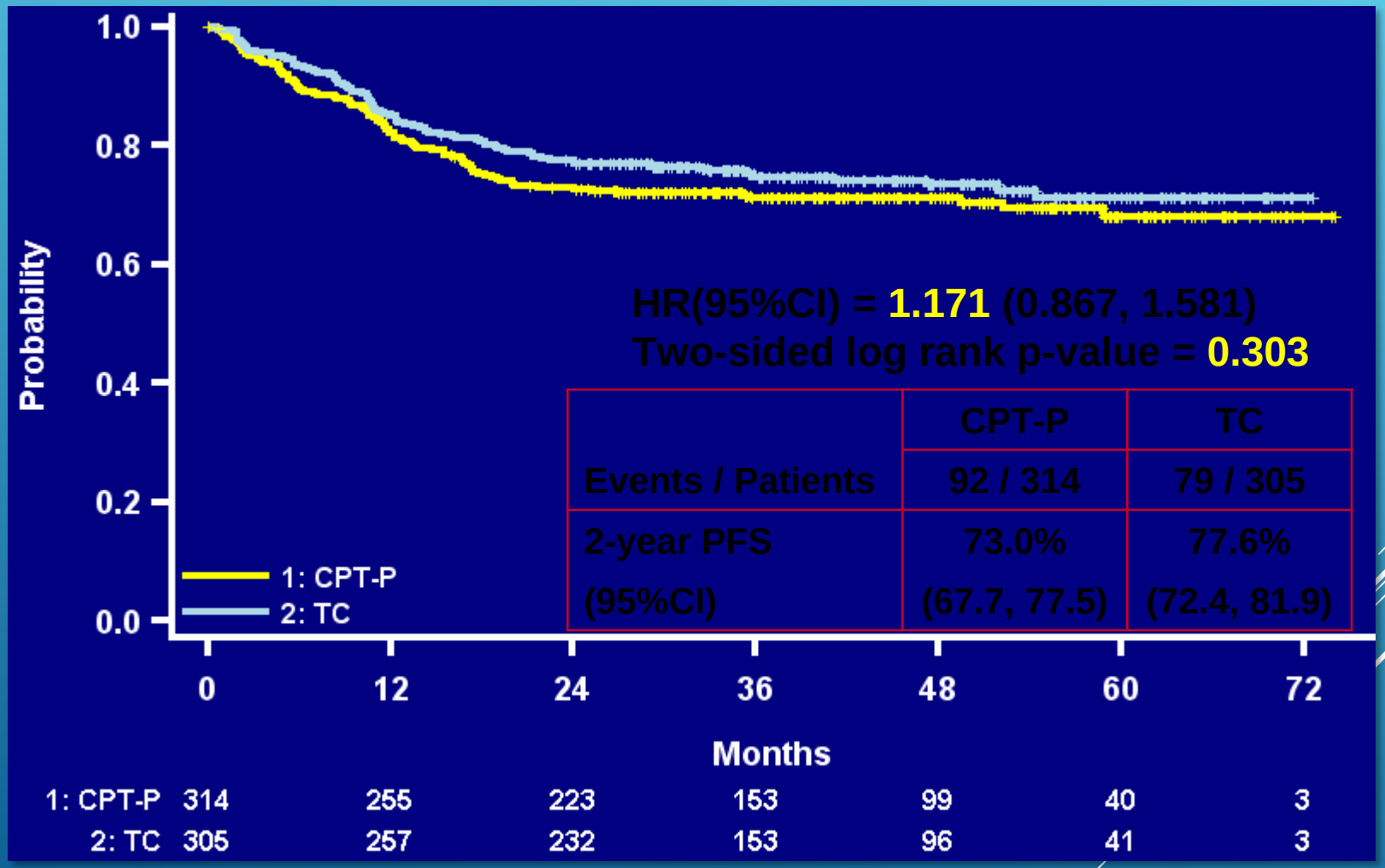
JGOG 3017/GCIG: Demographics & Baseline Characteristics

Demographics		TC(n=305)	CPT-P(n=314)
Age --- Median(Min-Max)		53y(30-81)	53y(30-75)
Race	**Japanese**	281(48.5%)	298(51.5%)
	Non-Japanese	24(60.0%)	16(40.0%)
Performance status (ECOG)	**0**	268(47.9%)	291(52.1%)
	1	37(61.7%)	23(38.3%)
Stage	**Ia-Ib**		
	Ic		
	II-IV		
Size of residual	**Complete**		
	Optimal (=<1cm)		
	Suboptimal (>1cm)		

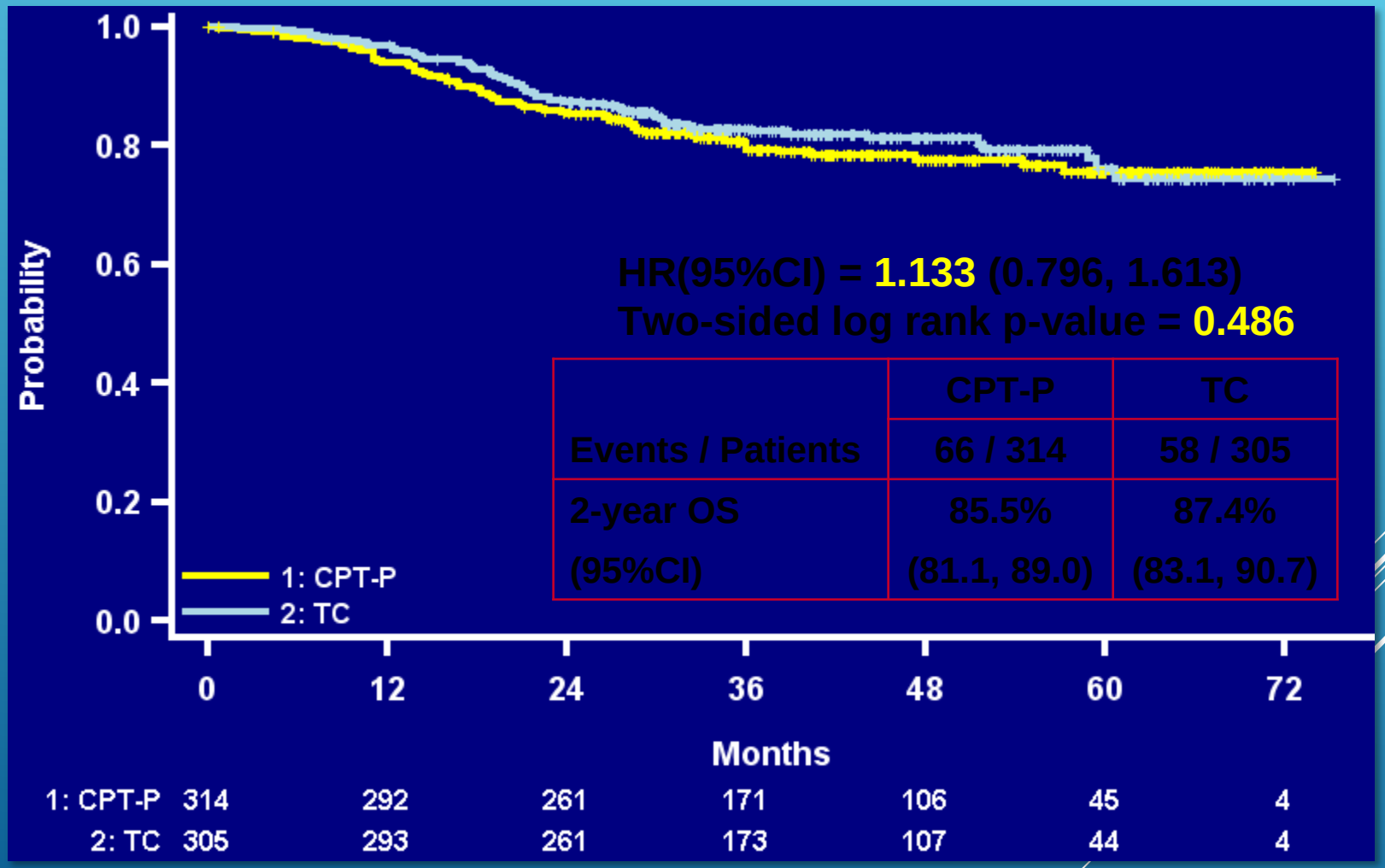
Stage I: 66.4%

Complete: 87.9%

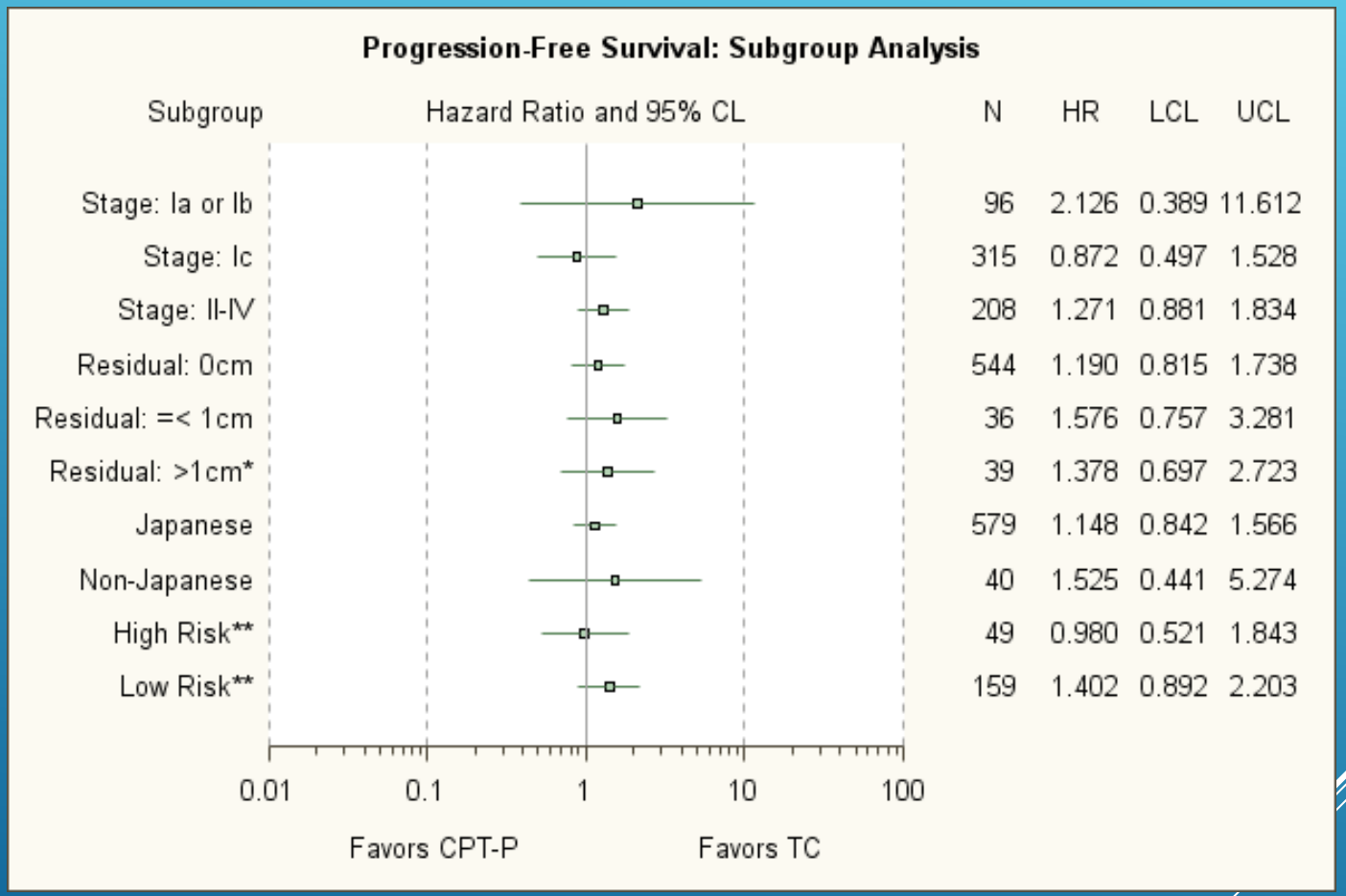
JGOG 3017: 2-year PFS for TC vs CPT-P



JGOG 3017: 2-year OS for TC vs CPT-P



JGOG 3017: PFS Subgroup Analysis

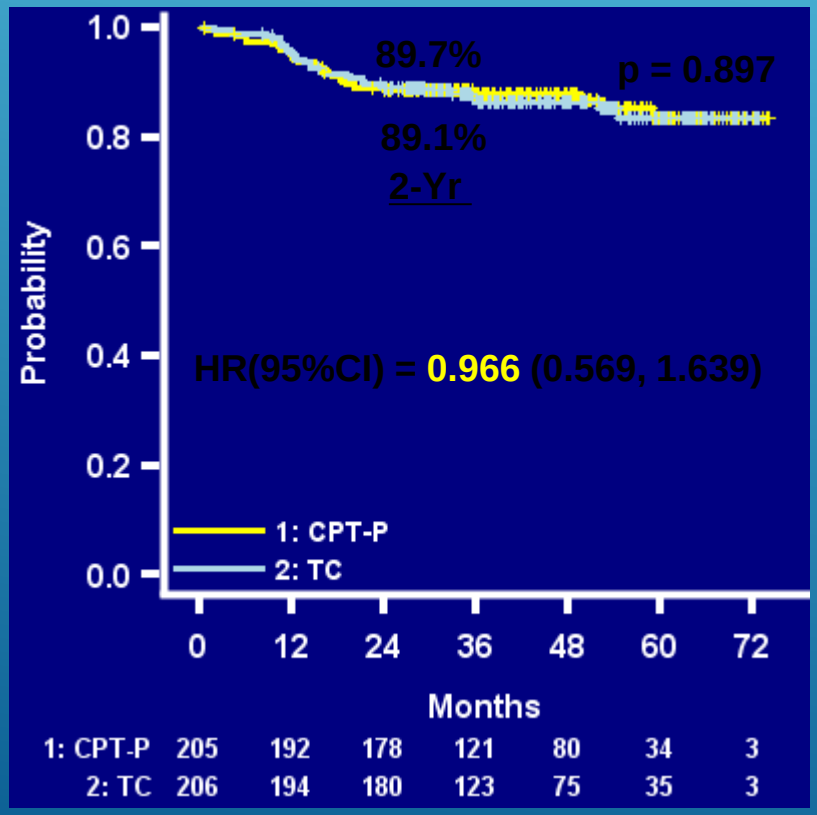


* Include stage IV patients

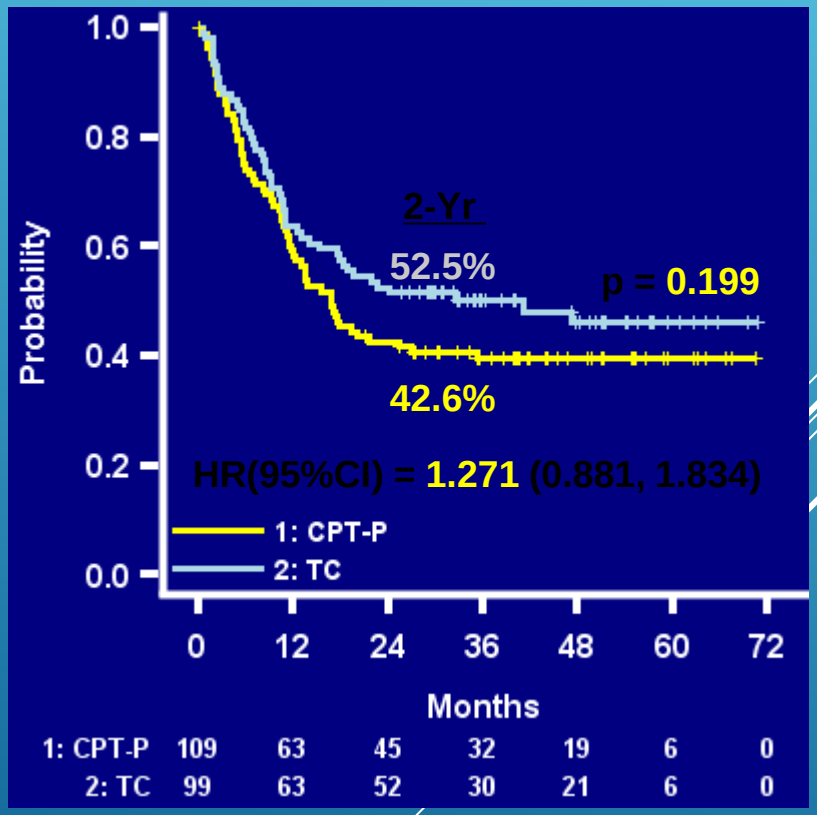
** High risk: suboptimal III + IV, Low risk: II + other III

PFS stage I vs stages II-IV

I



II-IV



JGOG 3017/GCIG: Summary

- With 44.3 months median follow-up, the 2-year PFS : 73.0% (95% CI:67.7-77.5) in the CPT-P arm vs. 77.6% (95% CI:72.4-81.9) in the TC arm were not significantly different (HR:1.171, 95% CI:0.867-1.581, p=0.303).

- Two-year OS was 85.5% in CPT-P arm (95% CI:81.1-89.0) and 87.4% in TC arm (95% CI:83.1-90.7), respectively (HR:1.133, 95% CI:0.796-1.613, p=0.486).

- Grade 3/4 leukopenia, neutropenia, thrombocytopenia, peripheral sensory neuropathy and joint pain occurred more frequently in the TC arm ($p<0.05$) , whilst grade 3/4 anorexia, diarrhea, nausea, vomiting and febrile neutropenia occurred more frequently in the CPT-P arm ($p<0.05$) .

JGOG 3017/GCIG: Conclusions

- In this first CCC-specific international clinical trial, a survival benefit was not observed by CPT-P.
- Paclitaxel with carboplatin remain to be a standard chemotherapy for CCC. However, since the toxicity profile is different, CPT-P can be an alternative choice of chemotherapy for CCC.

A randomized phase 2 trial comparing efficacy of the combination of the PARP inhibitor olaparib and the antiangiogenic cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer.

- Joyce Liu, William Thomas Barry, Michael J. Birrer, Jung-min Lee, Ronald J. Buckanovich, Gini F. Fleming, Bj Rimel, Mary K. Buss, Sreenivasa R. Nattam, Jean Hurteau, Weixiu Luo, Philippa Quy, Elizabeth Obermayer, Christin Whalen, Hang Lee, Eric P. Winer, Elise C. Kohn, S. Percy Ivy, Ursula Matulonis; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; National Cancer Institute, National Institutes of Health, Bethesda, MD; University of Michigan, Ann Arbor, MI; University of Chicago Medical Center, Chicago, IL; Cedars Sinai Medical Center, Los Angeles, CA; Beth Israel Deaconess Medical Center, Boston, MA; Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN; Northshore University Health Systems, University of Chicago, Evanston, IL; IBCSG Statistical Center, Dana-Farber Cancer Institute, Boston, MA; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD

Presented by:

Olaparib versus Olaparib and Cediranib

- **Background**

- PARP inhibitors and anti-angiogenics are clinically active in recurrent ovarian cancer (OvCa).
- Preclinical studies suggest these agents can synergize, and a phase 1 study showed that the combination of cediranib (ced) and olaparib (olap) is well-tolerated.
- We therefore compared the activity of olap alone (Olap) to combined ced and olap (Ced/Olap) in treatment of recurrent platinum-sensitive (plat-sens) high-grade serous (HGS) or BRCA-related OvCa (NCT 01116648).

Methods

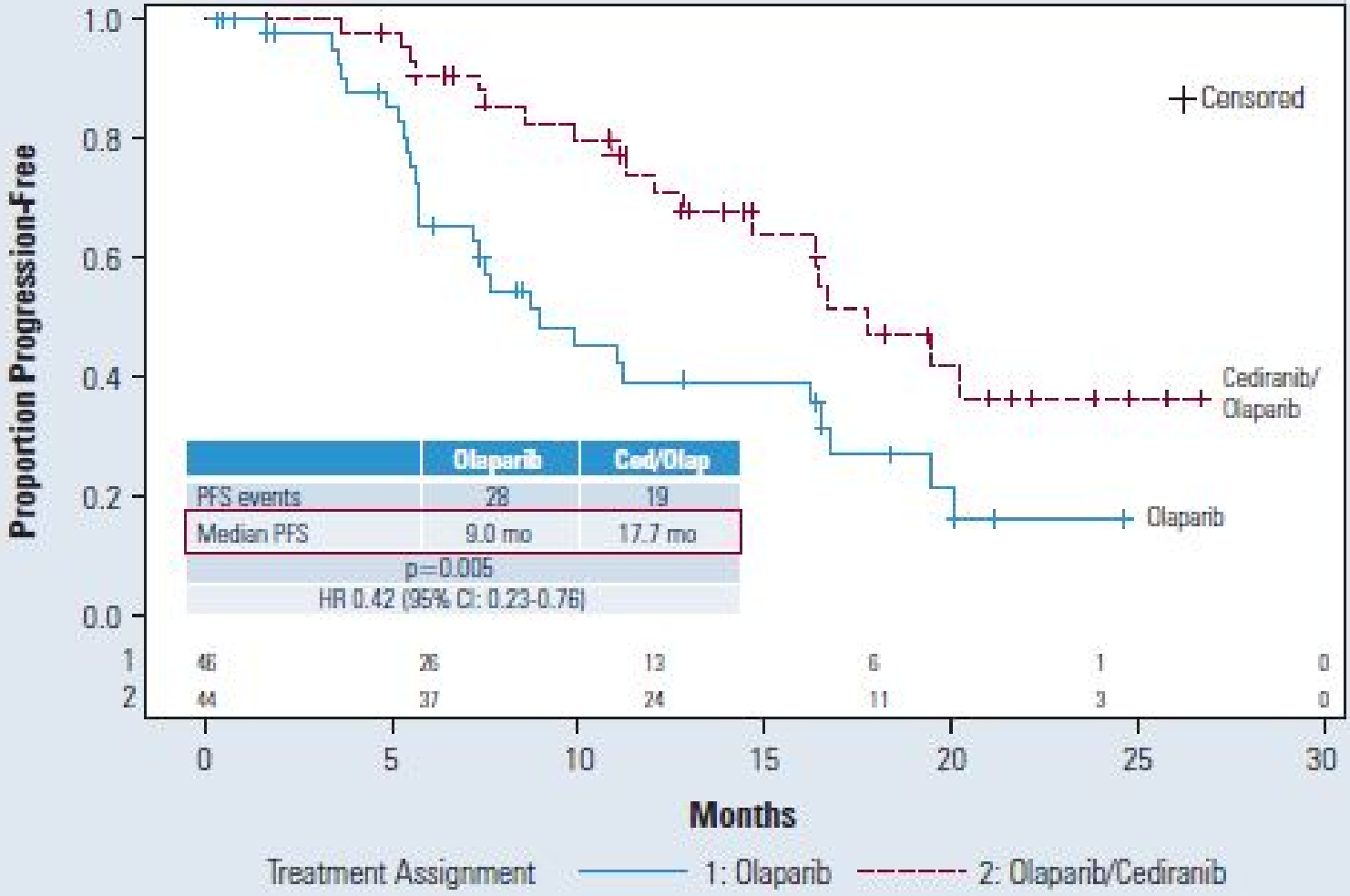
- Patients (pts) across 9 centers were randomized 1:1 in this Ph 2 open label study to Olap (olap 400 mg capsules BID) or Ced/Olap (olap 200 mg capsules BID; ced 30 mg daily),
- Stratified by BRCA status and prior anti-angiogenic therapy.
- Eligibility included pts with recurrent plat-sens HGS or BRCA-related OvCa.
- Pts had measurable disease by RECIST 1.1, PS 0 or 1, and the ability to take POs. No prior anti-angiogenics in the recurrent setting or prior PARP inhibitor was allowed.
- Progression-free survival (PFS) was defined as time from randomization to radiographic progression or death. With a target N=90 pts, the study was powered to detect a hazard ratio (HR) of 1.75 (median PFS 6 vs 10.5 mo).

Results

- Pts were enrolled from Oct 2011 to Jun 2013: 46 to Olap, 44 to Ced/Olap.
- 48 pts were known BRCA carriers (25 Olap; 23 Ced/Olap).
- Median Follow up was 16.6 months
- Median PFS was 9.0 mos for Olap and 17.7 mos for Ced/Olap (HR 0.42, 95% CI 0.23-0.76, p = 0.005).
- There were 2 complete responses (CR) and 20 partial responses (PR) in pts on Olap (56% objective response rate, ORR) and 5 CRs and 30 PRs in pts on Ced/Olap (84% ORR, p = 0.002)
- Responses based only on RECIST

Fig. 1

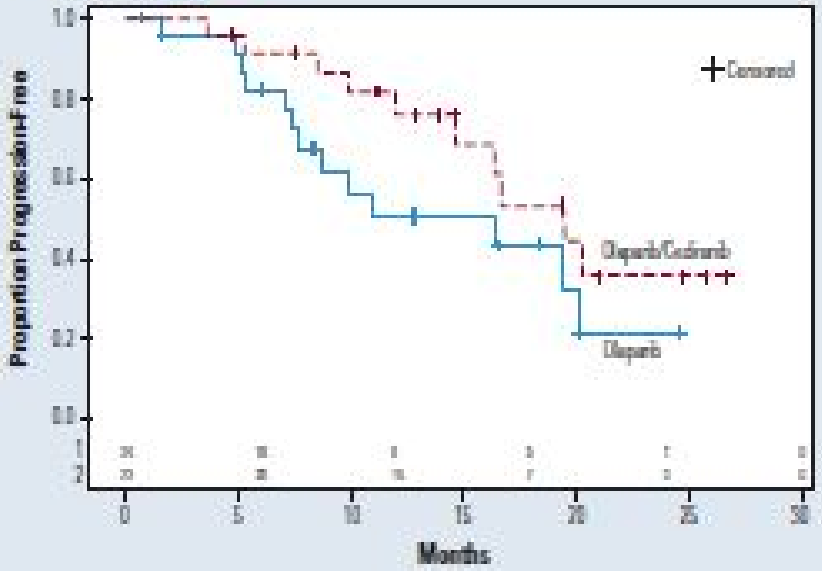
Primary Outcome: Cediranib/Olaparib Significantly Increased PFS Compared to Olaparib Alone



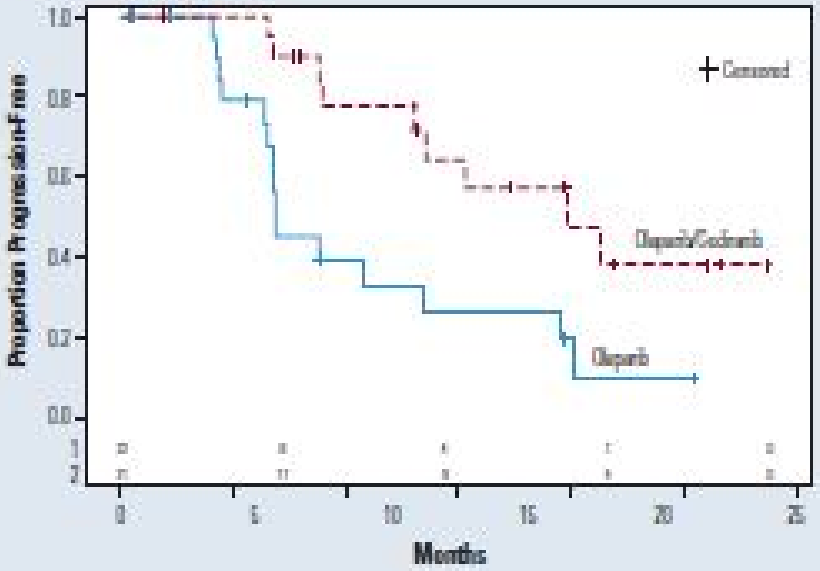
Presented by:

Fig. 2 Cediranib/Olaparib Significantly Increased PFS in Patients without a *BRCA* Mutation

***BRCA* mutation carrier**



***BRCA* non-carrier/unknown**



Treatment Assignment — 1: Olaparib - - - 2: Olaparib/Cediranib

	BRCA Mutation Carrier		*BRCA* Non-Carrier/Unknown	
	Olaparib	Ced/Olap	Olaparib	Ced/Olap
PFS events:	13	10	15	9
Median PFS	16.6 mo	19.4 mo	5.7 mo	16.5 mo
	p=0.16		p=0.008	
	HR 0.55 (95% CI: 0.24-1.27)		HR 0.32 (95% CI: 0.14-0.74)	

Presented by:

Toxicity

- The overall rate of Gr3/4 toxicity was higher for pts on Ced/Olap
- Non Hematological toxicity
- Gr 3 or more

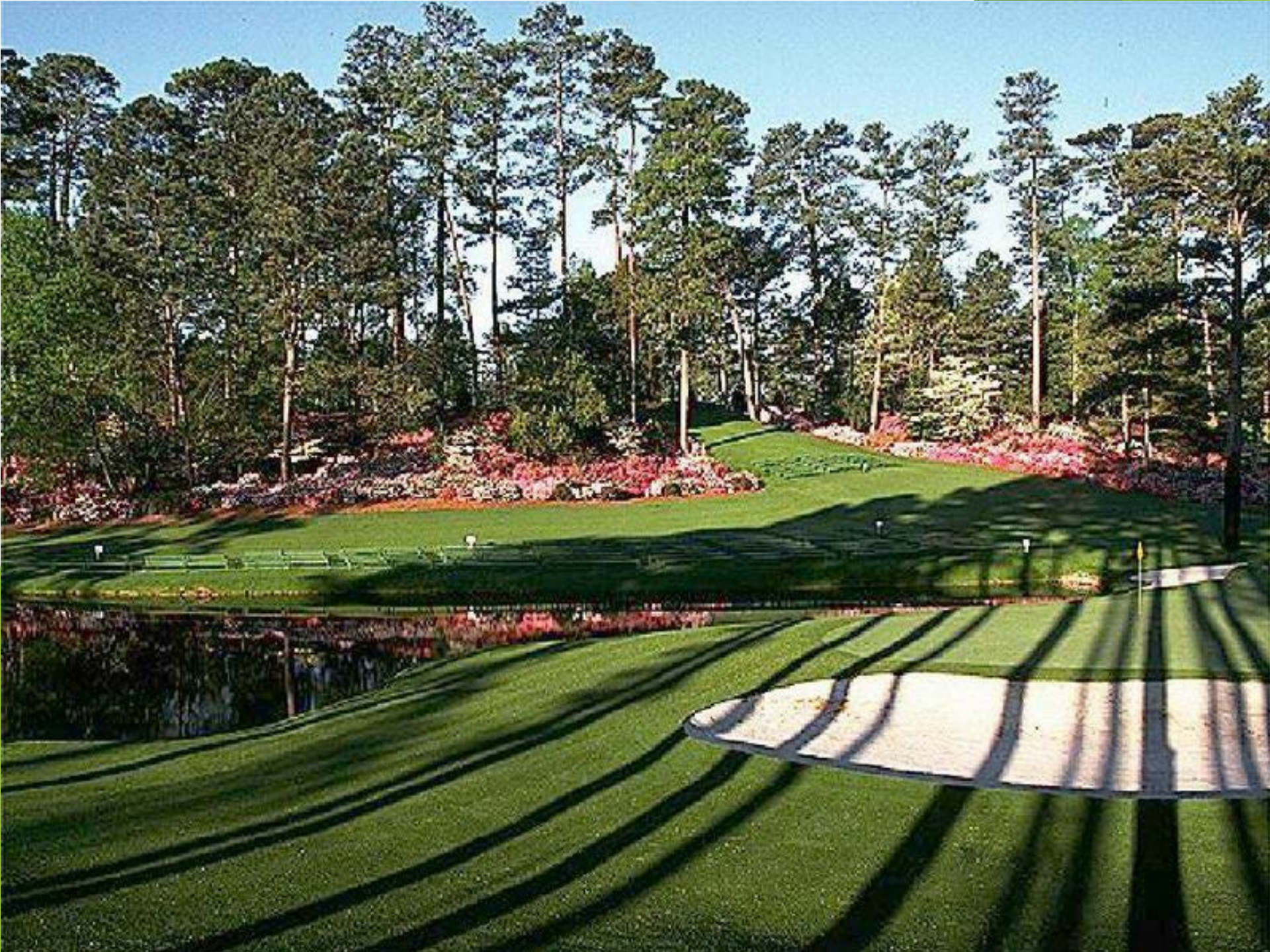
	Olap	Ced/Olap
Fatigue	11%	27%
HTN	0 %	41%
Diarrhea	0%	23%

- Dose reductions in 77% of pts in combination arm

Conclusions

- Combination of Ced/Olap has significant activity in platinum sensitive, recurrent high grade serous and BRCA positive ovarian cancer, especially in patients with wild type/unknown/negative BRCA status
- Significant non hematological toxicity that requires proactive management and dose reductions

Presented by:

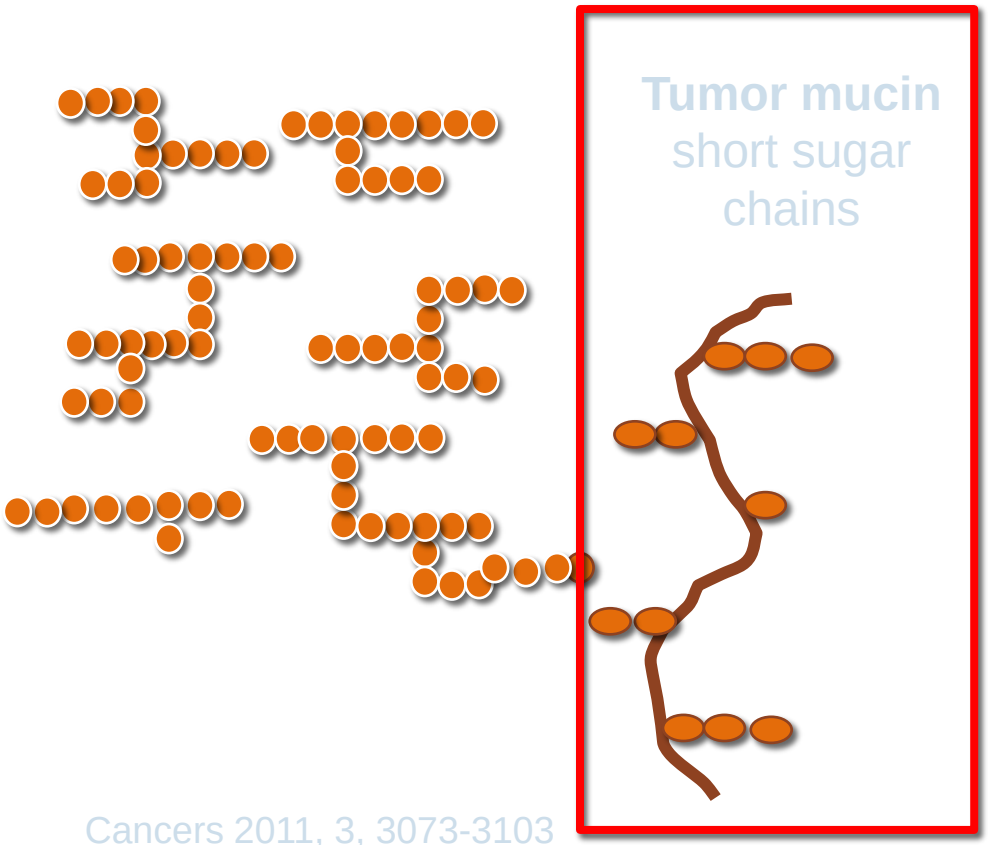


PROGRESSION-FREE SURVIVAL IN OVARIAN CANCER PATIENTS IN SECOND REMISSION IS IMPROVED WITH MUCIN 1 AUTOLOGOUS DENDRITIC CELL THERAPY (CAN-003)

HEIDI J. GRAY, MD

ASSOCIATE PROFESSOR
UNIVERSITY OF WASHINGTON MEDICAL CENTER
FRED HUTCHINSON CANCER RESEARCH CENTER,
SEATTLE, WA, USA
ASCO ANNUAL MEETING
MAY 31, 2014

Mucin 1; an optimal target for Immunotherapy

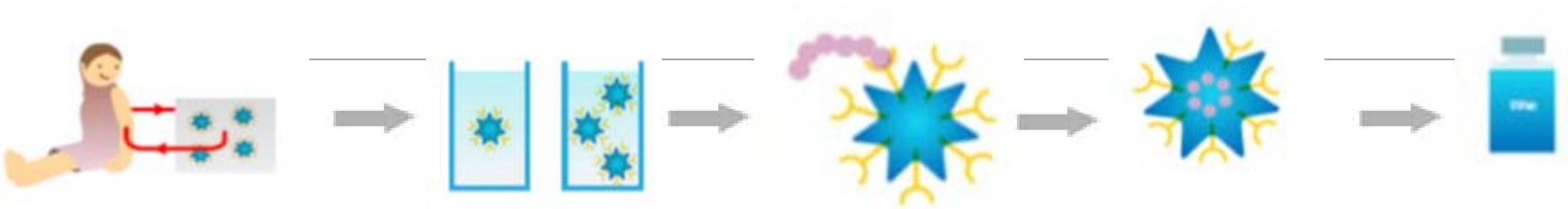


Cancers 2011, 3, 3073-3103

Nasopharyngeal	100%
Lung (NSCLC)	99%
Breast	91%
Renal	84%
Ovarian	**83%**
SCC HN	82%
Colorectal	81%
Pancreatic	81%
Prostate	79%
Myeloma	73%

Cvac – dendritic cell immunotherapy

Manufacturing of Cvac



MNCs (white blood cells) collection

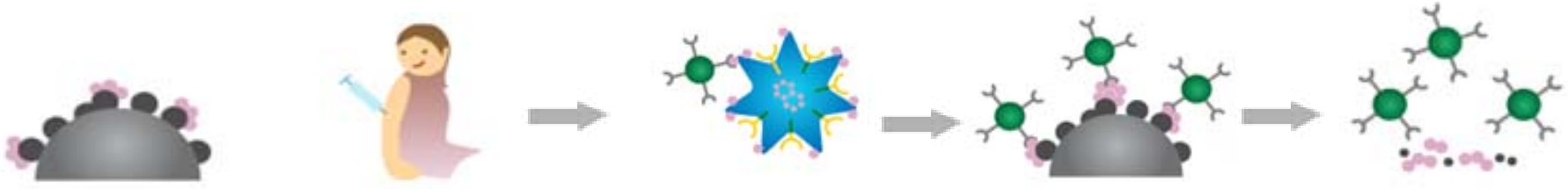
MNCs are separated and matured to DC

DCs are treated with mucin

Mucin 1 internalised

Formulated, and frozen in 1 mL vials = CVac

Mechanism after injection



Mucin 1 on cancer caells

Cvac is administered 4 ID per dose

Cvac activates Tcells

T cells target mucin 1 - cancer cells

T cells kill cancer cells

Cvac Prior Studies in Humans

Study	Indication	Product & Route	No. Patients	Outcome
CAN-001 (Phase 1)	Adenocarcinoma	Cvac ID	14	Safety
CAN-002 (Phase 2)	Epithelial ovarian carcinoma	Cvac ID	28	Safety
CAN-003 (Phase 2)	Epithelial ovarian carcinoma (CR1 and CR2 remission)	Cvac ID	63	Safety and Efficacy
CAN-003X (Phase 2)	Epithelial ovarian carcinoma (CR1 and CR2 remission)	Cvac ID	9	Safety

CAN-003:
Randomized open label, phase 2 trial

Purpose:

- Determine the safety and efficacy of Cvac vs Observational Standard of Care in patients with First or second remission

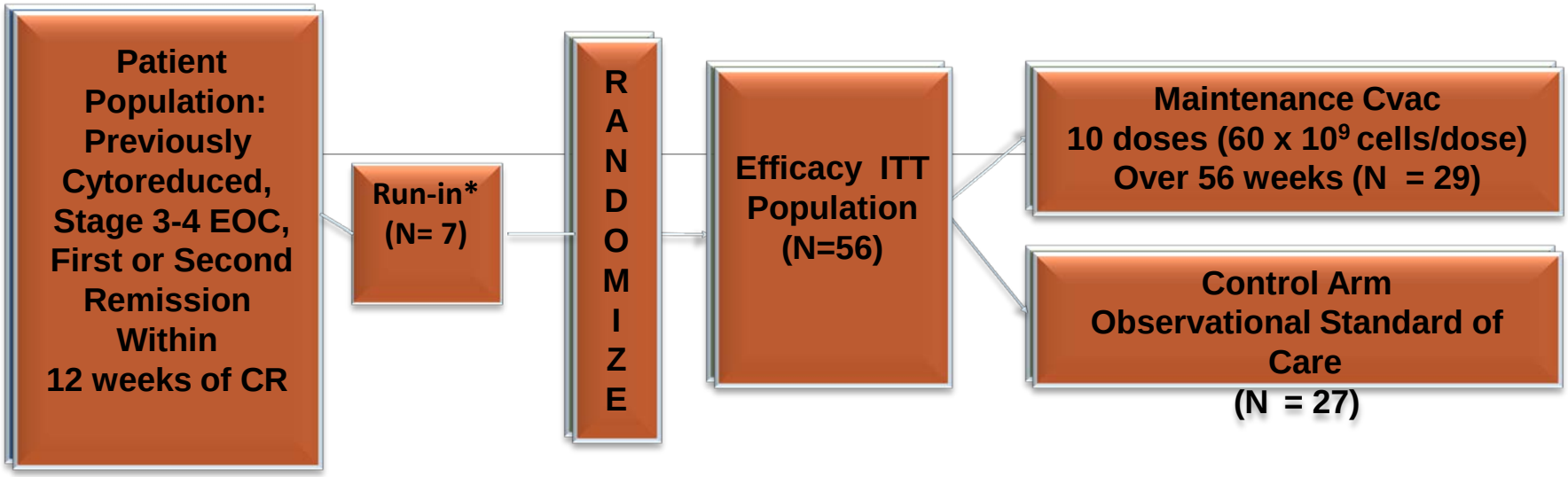
Primary Objectives:

- Safety
- Progression-free survival (PFS)

Secondary Objectives:

- Overall survival (OS)
- Immunologic response (humoral and cellular)

CAN-003 Study Design



CAN-003 Eligibility Criteria

Primary Inclusion

Stage III or IV

- Histologically confirmed epithelial ovarian, primary peritoneal or fallopian tube cancer

Complete remission (CR)

- following surgical cytoreduction and received first or second line conventional chemotherapy.

CA-125 ≤ ULN with a prior history of an elevated CA-125

Not more than 12 weeks between enrollment and the last dose of chemotherapy that resulted in a confirmation of a CR

ECOG 0 to 1

Primary Exclusion

Ovarian germ cell, carcinoma-sarcoma, or mixed Mullerian tumors.

CAN-003 Statistical Design

Planned sample size of 60 patients

Designed to assess feasibility & preliminary efficacy/safety

ITT= all patients who underwent randomization (N=56)

Randomization stratified on remission status (CR1, CR2)

PFS measured from randomization date

summarized descriptively using Kaplan-Meier method and log-rank test. Hazard ratio (Cvac/SOC) estimated using Cox model

CAN-003 Results: Demographics

Characteristic	CVAC (N=29)	SOC (N=27)
Remission status		
Achieved after first-line therapy (CR1)	19 (66%)	17 (63%)
Achieved after second-line therapy (CR2)	10 (34%)	10 (37%)
Disease stage		
III	24 (83%)	20 (74%)
IV	5 (17%)	7 (26%)
Histology subtype		
Serous	25 (86%)	23 (85%)
Endometrioid	1 (3%)	2 (7%)
Mucinous	1 (3%)	1 (4%)
Other (mixed, not specified)	2 (7%)	1 (4%)
Cytoreduction/debulking surgery		
Optimal	27 (93%)	23 (85%)
Suboptimal	2 (7%)	4 (15%)
Age years		
median (range)	58 (34-75)	49 (43-70)

CAN-003 Safety

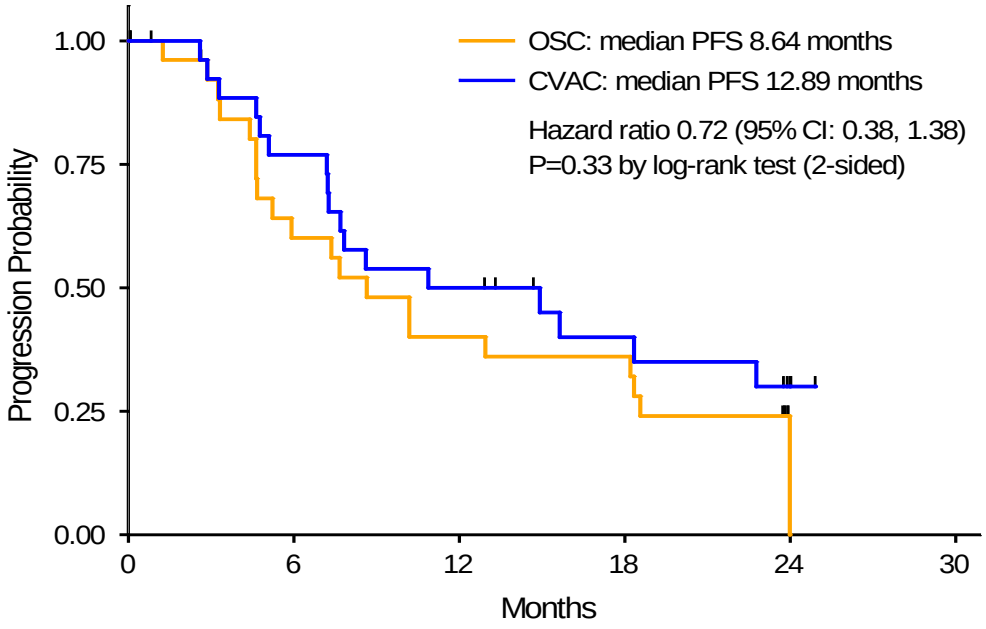
	N	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
First remission(CR1)	32	9 (28%)	14 (44%)	7 (22%)	0 (0%)	0(0%)
SOC	14	5 (36%)	7 (50%)	1 (7%)	0 (0%)	0 (0%)
Cvac	18	4 (22%)	7 (39%)	6 (33%)	0 (0%)	0 (0%)
Second remission (CR2)	18	12 (67%)	3 (17%)	2 (11%)	0 (0%)	0 (0%)
SOC	10	7 (70%)	1 (10%)	1 (10%)	0 (0%)	0 (0%)
Cvac	8	5 (63%)	2 (25%)	1 (13%)	0 (0%)	0 (0%)

Common AEs - symptoms at injection site (localized pain, erythema, redness, swelling, burning), events of fatigue, lethargy, and dizziness were also reported as related to study agent

CAN-003 T cell Immune Monitoring

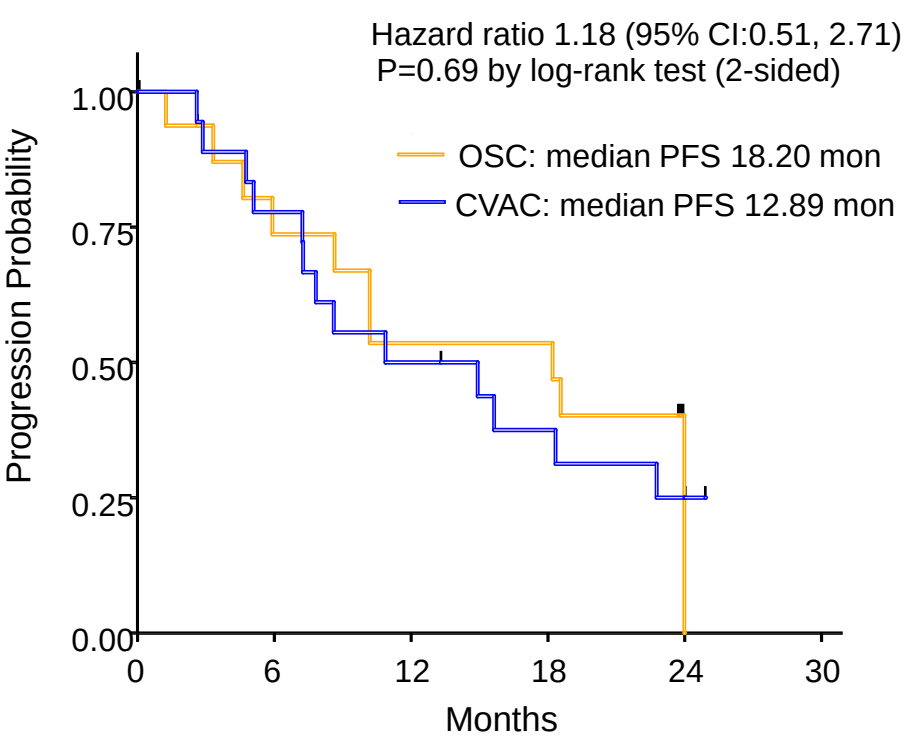
	CD4 IL-2	CD4 IL-4	CD4 IFNg	CD4 TNFa	CD4 IL-17
1st Remission CR1	*	*	*		
2nd Remission CR2	**	**	*		
Overall					
	CD8 IL-2	**CD8 IL-4**	**CD8 IFNg**	**CD8 TNFa**	**CD8 IL-17**
1st Remission CR1	*	**		**	
2nd Remission CR2		*		*	**
Overall		*	*		*

CAN-003 Progression-Free Survival (ITT, n=56)



CAN-003 Comparison of PFS

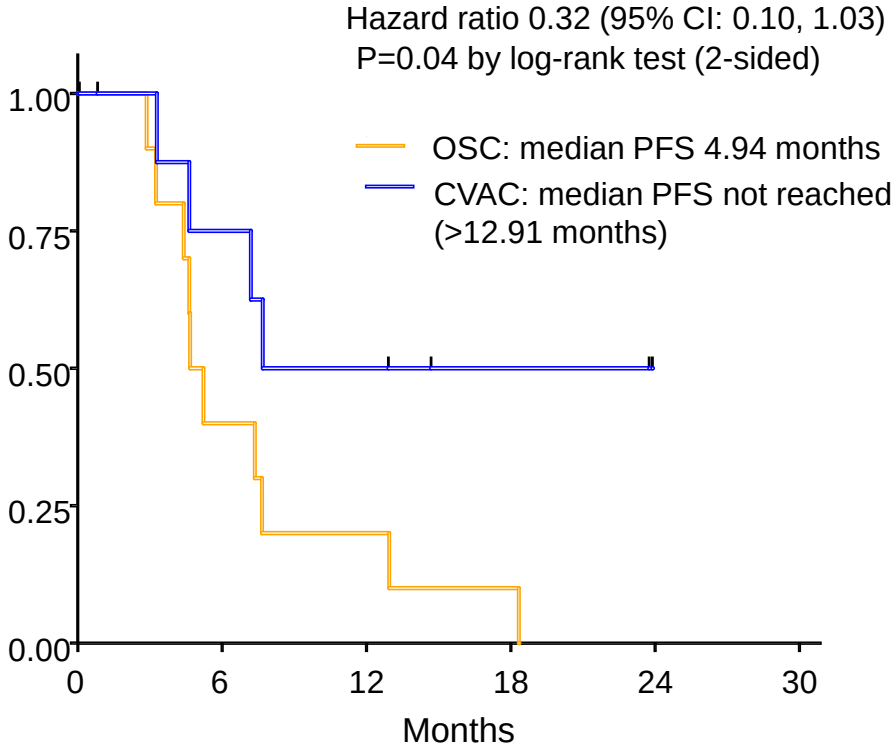
FIRST REMISSION CR1



OSC	4/17	3/11	0/8	3/8	0/0
CVAC	4/19	5/14	2/9	2/6	0/3

(#events/#at risk)

SECOND REMISSION CR2



OSC	6/10	2/4	1/2	1/1	0/0
CVAC	2/10	2/6	0/4	0/2	0/0

(#events/#at risk)

CAN-003 Conclusions

Feasibility - Multinational manufacture and distribution of Cvac was possible

Safe - Cvac was well tolerated with minimal toxicity

Immunogenic - Positive mucin 1-specific T cell response in CVac treated patients

PFS signal in second remission

Interim OS signal in second remission

IMPACT OF VAGINAL DEHYDROEPIANDOSTERONE (DHEA) ON VAGINAL SYMPTOMS IN CANCER SURVIVORS TRIAL N10C1 (Alliance)

Debra Barton RN, PhD, AOCN, FAAN
Professor, University of Michigan School of Nursing

Patient/Survivor Care Oral Session

ASCO, 2014

Presented by:

Predictors of Sexual Health

- Breast Cancer Survivors –
  body image, mental health, new partner
  vaginal dryness, past chemotherapy

Ganz, JCO, 1999

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More Predictors

- Gynecologic survivors:

  lack of partner, lack of interest,

  fatigue, physical problems

  (vaginal dryness, dyspareunia)

Carmack Taylor, JCO, 2004

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Estrogen Vaginal Pharmacology

- Changes in vaginal tissues due to decrease in estrogen:
  - loss of rugae and thickening of vaginal wall
  - thinner mucosa (thinner and pale)
  - Fewer epithelial cells, lower # superficial cells, more basal and parabasal cells
  - increased pH
- Bartholin's glands secrete less fluid

(da Silva Lara et al. J Sex Med, 6:30-39, 2009)

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"THIS IS A 'PLACEBO' LINE. IT SERVES NO PURPOSE BUT IT MAKES US FEEL GOOD."

Evidence Based Interventions

- Water soluble or silicone based lubricants
- Vaginal moisturizers
- Vaginal estrogen

(Goldfarb et al. Semin Oncol 40:726-744, 2013; North American Menopause Position Statement on the management of symptomatic vulvovaginal atrophy, Menopause, 20:888-902, 2013)

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Types of Vaginal Estrogen

- Cream: 0.5 – 4 grams
- Tablet: 10 micrograms over 24 hours
- Ring: 7.5 micrograms over 24 hours active for 90 days

Most guidelines instruct to use more frequently first two weeks, then less often

(Goldfarb et al, Sem Oncol, 40(6), 2013; Tan et al, Menopause, 19(1), 2012)

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Issues with Vaginal Estrogen

- Results for estrogen ring (7.5 mcg)
- Systemic concentrations increased but remain in post menopausal range
- Changes in lipids: HDL, LDL, total chol, apoB
- Changes in bone biomarkers: osteocalcin and bone alkaline phosphatase

(Naessen, J Clin End Metab, 2001; Naessen, Am J ObGyne, 1997; Handa, OBGyne, 1994; Labrie, Menopause, 2009)

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DHEA

- Made by adrenal gland - prohormone
- Decreases with age (not menopause)
- Converted mostly in target tissue to estrogen or androgen

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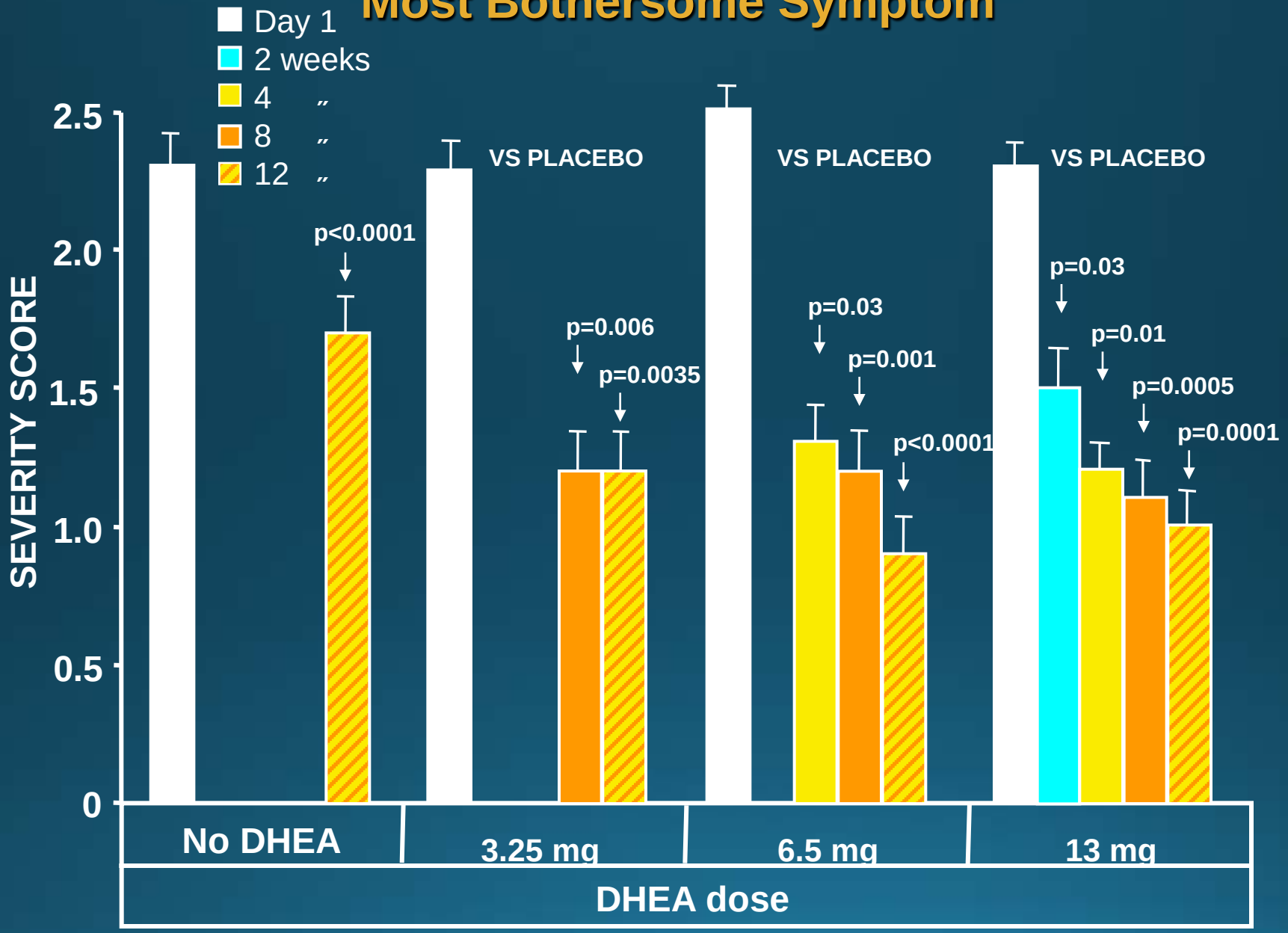
Most Bothersome Symptom



Labrie, Archer et al, Menopause, 2009

Objectives

- Determine the effectiveness of two doses of vaginal DHEA for the improvement of the most bothersome vaginal symptom: dryness or dyspareunia

- Evaluate the side effects of this treatment

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N10C1 Alliance Trial
Registration and randomization

DHEA 3.25 mg in bioadhesive moisturizer base

DHEA 6.5 mg in bioadhesive moisturizer base

Bioadhesive moisturizer base alone

Each treatment taken daily at bedtime for 12 weeks

Presented by:

Inclusion Criteria

- Post menopausal women, history of breast/gynecologic cancer (NED)
- FSH and estradiol value in the postmenopausal range (generally FSH >40 IU/L and estradiol < 10 pg/ml
- At least moderately severe vaginal complaints present at least 2 months

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Exclusion Criteria

- Prior or concurrent pelvic radiation therapy, prior radical pelvic surgery, (TAH/BSO is allowed)

- No vulvar/vaginal dysplasia or diseases (ie: infections, lichen sclerosis or planus or Bartholin gland abnormalities)

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Other Criteria

- Newly on endocrine treatment (8 weeks required without planned change)
- Vaginal preparations other than water based lubricant for intercourse

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Translational Study Funded by Breast Cancer Research Foundation

- Blood being drawn for sex steroid hormone levels and markers of bone turnover (all)

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Our DHEA Intervention

- Gel made by compounding pharmacist
- IND 111454
- Administration by prefilled syringes
- One syringe before bed x 12 weeks

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Outcome Measures Related to Intervention

- Primary: Most bothersome symptom: dryness or dyspareunia
- Secondary: Female Sexual Function Index, DHEA side effect questionnaire, overall QOL question, Subjective Global Impression of Change

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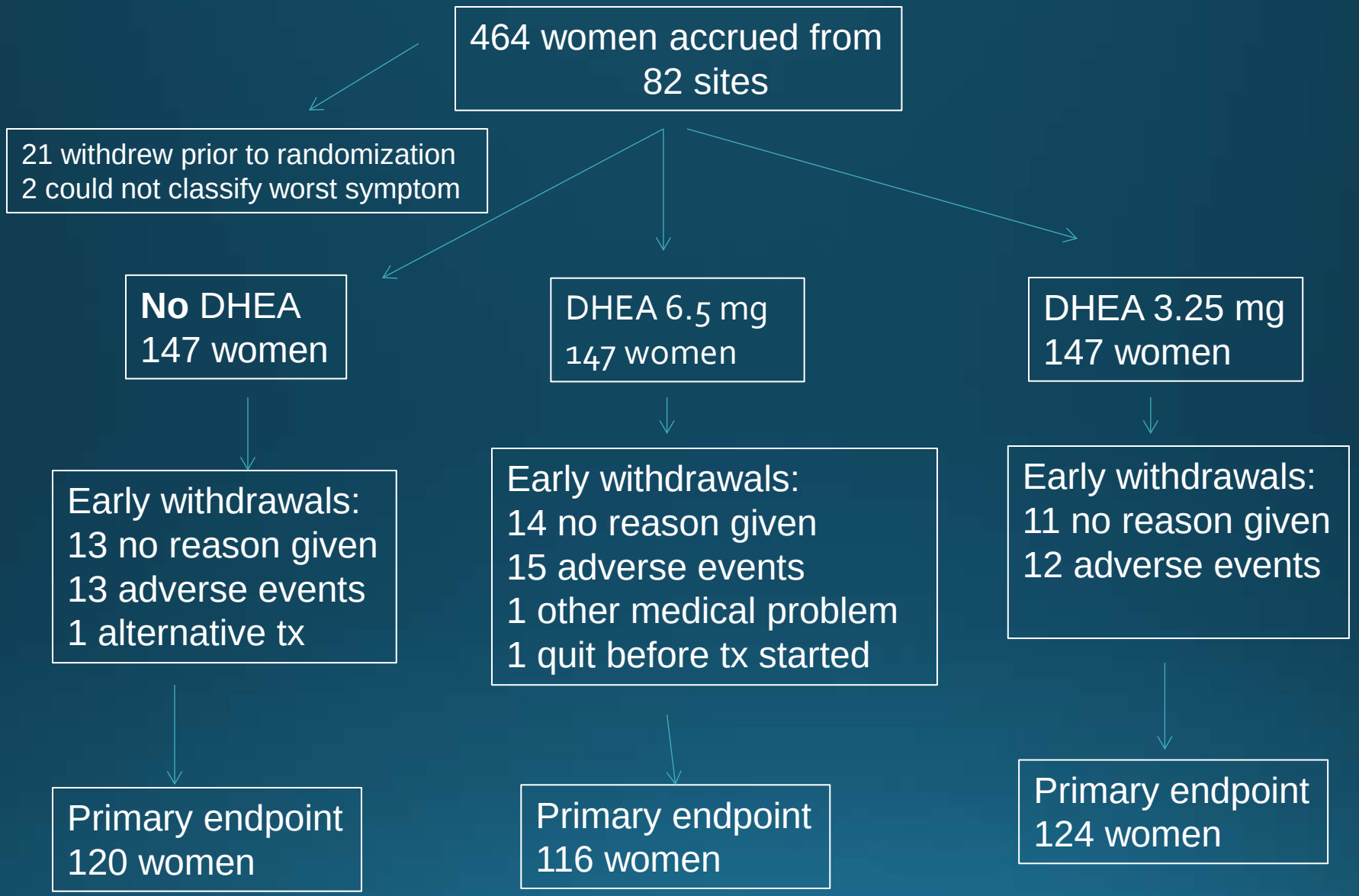
464 women accrued from 82 sites
21 withdrew prior to randomization
2 could not classify worst symptom
No DHEA
147 women
DHEA 6.5 mg
147 women
DHEA 3.25 mg
147 women
Early withdrawals:
13 no reason given
13 adverse events
1 alternative tx
Early withdrawals:
14 no reason given
15 adverse events
1 other medical problem
1 quit before tx started
Early withdrawals:
11 no reason given
12 adverse events
Primary endpoint
120 women
Primary endpoint
116 women
Primary endpoint
124 women

Analysis and Power

- Mean change from baseline to 12 weeks
- Two independent t-tests comparing each DHEA arm with moisturizer alone
- Bonferroni correction
- Type I error 2.5%
- 145 women/arm provided 80% power for 0.36 SD difference

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Demographic Characteristics

Characteristic	No DHEA	DHEA 3.25 mg	DHEA 6.5 mg	P Value
Age (SD)	58 (7.3)	56.8 (6.7)	57.3 (8.2)	0.63
Race				
White	137 (93%)	142 (97%)	142 (95%)	
Black/AA	7 (5%)	3 (2%)	5 (4%)	0.63
Asian	1 (1%)	0	0	
Menopause-natural	95 (65%)	98 (67%)	88 (59%)	0.37
Bilateral ooph	48 (33%)	43 (30%)	55 (37%)	0.38
Weight kg (SD)	74.8 (16.6)	76.6 (14.7)	73.2 (14.8)	0.06
Height (SD)	163.2 (6.6)	164.4 (6.0)	163.1 (6.8)	0.20

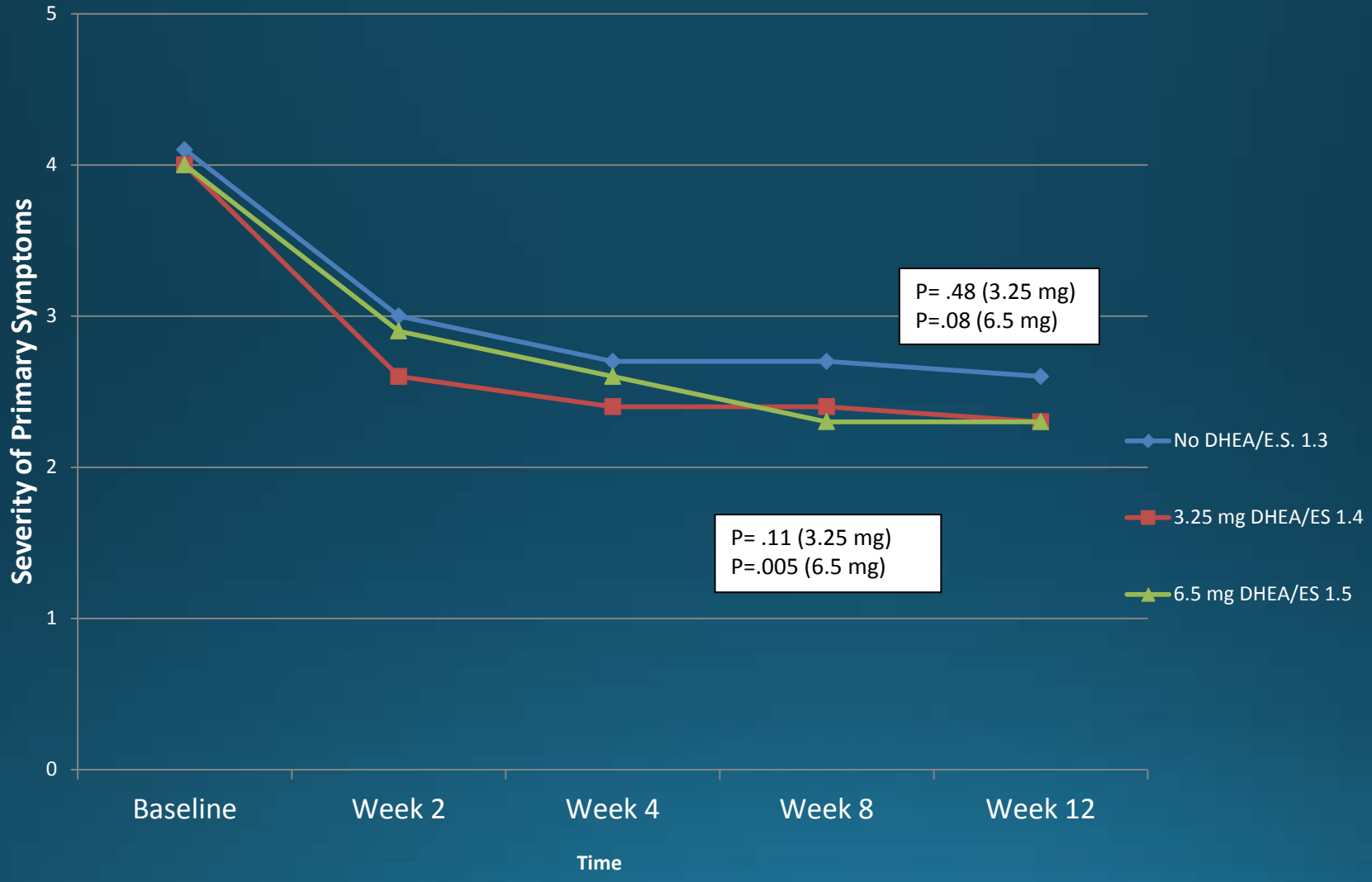
Treatment Characteristics

Characteristic	No DHEA	DHEA 3.25 mg	DHEA 6.5 mg	P Value
Cancer Breast ovarian endometrial	142 (97%) 3 (2%) 2 (1%)	143 (97%) 4 (3%) 0	144 (97%) 3 (2%) 2 (1%)	0.70
Tamoxifen current	23(16%)	22 (15%)	24 (16%)	0.96
AI Current anast/letro exemestane	72 (49%) 9 (6%)	71 (48%) 11 (8%)	72 (48%) 10 (7%)	1.0
Months on current therapy (SD)	22 (18.7)	21.1 (17.1)	24.5 (18)	0.31

Symptom Characteristics

Characteristic	No DHEA	DHEA 3.25 mg	DHEA 6.5 mg	P Value
Primary cause of distress dryness dyspareunia	72 (49%) 75 (51%)	58 (40%) 89 (60%)	61 (41%) 86 (59%)	0.22
Mean severity of primary symptom (SD)	4.1 (0.8)	4 (0.7)	4 (0.7)	0.25
Severity/bother of primary symptom (SD)	8.0 (1.5)	7.7 (1.5)	7.8 (1.4)	0.21
Months of vaginal symptoms (SD)	36.2 (41.4)	37.3 (41.3)	35.3 (34.2)	0.78

Primary Outcome Results at 12 weeks



Female Sexual Function Index

Higher = better function

FSFI Subscale Change from baseline	No DHEA Mean (SD)	3.25 mg DHEA Mean (SD)	6.5 mg DHEA Mean (SD)
Desire	0.2 (0.9)	0.3 (1.0)	0.5 (1.0)**
Arousal	0.4 (1.6)	0.7 (1.4)*	1.0 (.16)**
Lubrication	1.1 (1.7)	1.3 (1.8)	3.0 (2.0)*
Orgasm	0.7 (1.8)	0.8 (1.9)	1.0 (1.7)
Satisfaction	0.5 (1.5)	0.9 (1.5)	1.1 (1.6)*
Pain	1.0 (1.8)	1.4 (1.7)*	2.0 (1.6)***
Overall Total	3.8 (7.4)	5.5 (7.5)	7.1 (7.3)***

Significant difference than no DHEA: * ≤.05, **≤.01, ***≤.001

Overall Quality of Life

Negative Numbers Indicates Worsening

	No DHEA	DHEA 3.25 mg	DHEA 6.5 mg	P value**
Week 12: Mean change from Baseline (SD)	-0.3 (2.2)	0.2 (1.7)	0.3 (1.9)**	.01

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Subjective Impression of Change

	No DHEA	DHEA 3.25 mg	DHEA 6.5 mg	P value
# (%) Perceiving a moderate to very much better change	47 (40%)	67 (55%)	69 (58%)	0.01

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Adverse Events

Grade AE	No DHEA (N=147)		3.2 mg DHEA (N=147)		6.5 mg DHEA (N=149)		P-value
Any grade: yes	68.7%		69.4%		77.9%		0.15
Grade 2+= Yes	36.7%		29.9%		32.9%		0.46
Grade 3+= Yes	12.2%		6.1%		8.7%		0.18
Adverse Event	GR2#	GR3#	GR2#	GR3#	GR2#	GR3#	
Breast Pain	8	0	9	0	16	0	
Headache	20	0	19	2	10	0	
Hirsutism	0	0	0	0	9	0	
Urinary tract infection	6	2	4	1	3	0	
Vaginal discharge	13	0	5	0	9	0	
Vaginal Infection	5	0	3	1	7	0	
Vaginal inflammation/pain	2	0	4	0	4	0	

Self Reported Side Effects

Change from Baseline: Negative numbers are worse
*** Significantly different from "No DHEA"**

Side Effect	No DHEA Mean (SD)	3.25 mg DHEA Mean (SD)	6.5 mg DHEA Mean (SD)
Vaginal discharge	-0.7 (2.6)	-0.8 (2.3)	-0.7 (2.3)
Rash in vaginal area	0.1 (1.6)	0.1 (1.3)	-0.1 (0.8)
Unwanted hair growth	0.7 (2.4)	0.4 (2.1)	0.3 (1.7)
Unwanted hair loss	0.3 (1.9)	0.0 (1.5)	0.2 (1.5)
Change in voice	0.2 (1.2)	-0.1 (0.7)*	-0.2 (1.1)*
Acne	0.1 (1.5)	-0.2 (1.8)	-0.3 (1.9)
Headaches	0.5 (2.2)	-0.2 (2.0)*	-0.1 (2.2)
Breast pain	0.3 (1.6)	0.3 (1.5)	0.4 (1.8)

***Significantly different from placebo**

Hormone Concentrations

*significantly different from "No DHEA"

Variable	No DHEA N=147	3.25 mg N=142	6.5 mg N=144
DHEA-S			
Pre	70.3 (41.9)	80.5 (47.7)	74.7 (50.8)
Post	70.3 (46.6)	96.2 (52.2)*	103.4 (56.3)*
Change	0	15.7 (27.2)*	28.8 (31)*
Estradiol			
Pre	3.5 (2.3)	3.6 (2.5)	3.6 (2.3)
Post	3.7 (3.3)	4.7 (6.4)	4.0 (2.8)
Change	0.2 (2.5)	0.9 (5.0)*	0.6 (1.9)*

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Hormone Concentrations

*significantly different from "No DHEA"

Variable	No DHEA N=147	3.25 mg N=142	6.5 mg N=144
Total Testosterone			
Pre	17.8 (9.6)	16.8 (8.7)	16.4 (10.7)
Post	17.6 (9.1)	21.1 (10.9)*	24.7 (13.1)*
Change	-0.1 (5.6)	4.4 (6.3)*	8.3 (10.5)*
Free Testosterone			
Pre	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)
Post	0.3 (0.2)	0.5 (0.3)*	0.5 (0.3)*
Change	0 (0.2)	0.1 (0.2)*	0.2 (0.2)*

Hormone Concentrations

*significantly different from "No DHEA"

Variable	No DHEA (N=147)	3.25 mg (N=142)	6.5 mg (N=144)
Bone Alkaline Phosphatase			
Pre	33 (11.5)	32.2 (13.5)	31.6 (11.9)
Post	34.6 (12.9)	35.5 (14.5)	32.9 (12)
Change	1.6 (7.4)	3.3 (9.3)	1.3 (8.4)
Osteocalcin			
Pre	20.1 (8.9)	20.6 (8.7)	19.9 (8.6)
Post	20.5 (9.5)	20.4 (8.8)	19.6 (8.8)
Change	0.4 (5.1)	-0.2 (5.7)	-0.1 (4.9)

Lab Values by AI Use

Variable	No DHEA		3.25 mg		6.5 mg	
Change from baseline	AI	No AI	AI	No AI	AI	No AI
DHEAS	-1.6 (17.2)	1.6 (37.5)	11.4 (19.7)*	21.6 (34.2)*	24.1 (34.1)*	34 (26.4)*
Estradiol	0.3 (3.3)	0.1 (1.4)	0 (0.3)	2.1 (7.6)*	-0.2 (0.7)	1.4 (2.4)*
Free Testosterone	0 (0.2)	0 (0.1)	0.1 (0.2)*	0.1 (0.1)*	0.2 (0.2)*	0.2 (0.2)*

*significantly different than “No DHEA”

Summary/Conclusions

- Daily bioadhesive moisturizers (not PRN use) improve vaginal symptoms of dryness or pain and pH
- DHEA 6.5 mg improved symptoms more quickly and to a non-significant greater degree
- DHEA 6.5 mg improved sexual function and overall QOL beyond what a moisturizer could

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Conclusions

- Vaginal DHEA is absorbed vaginally
- Though overall significant increases in estrogens were found, the 12 week values between arms were not significantly different
- Bone biomarkers did not change clinically or significantly
- All arms were equally well tolerated aside from significant differences in voice changes (both DHEA doses) and headaches (3.25 mg)

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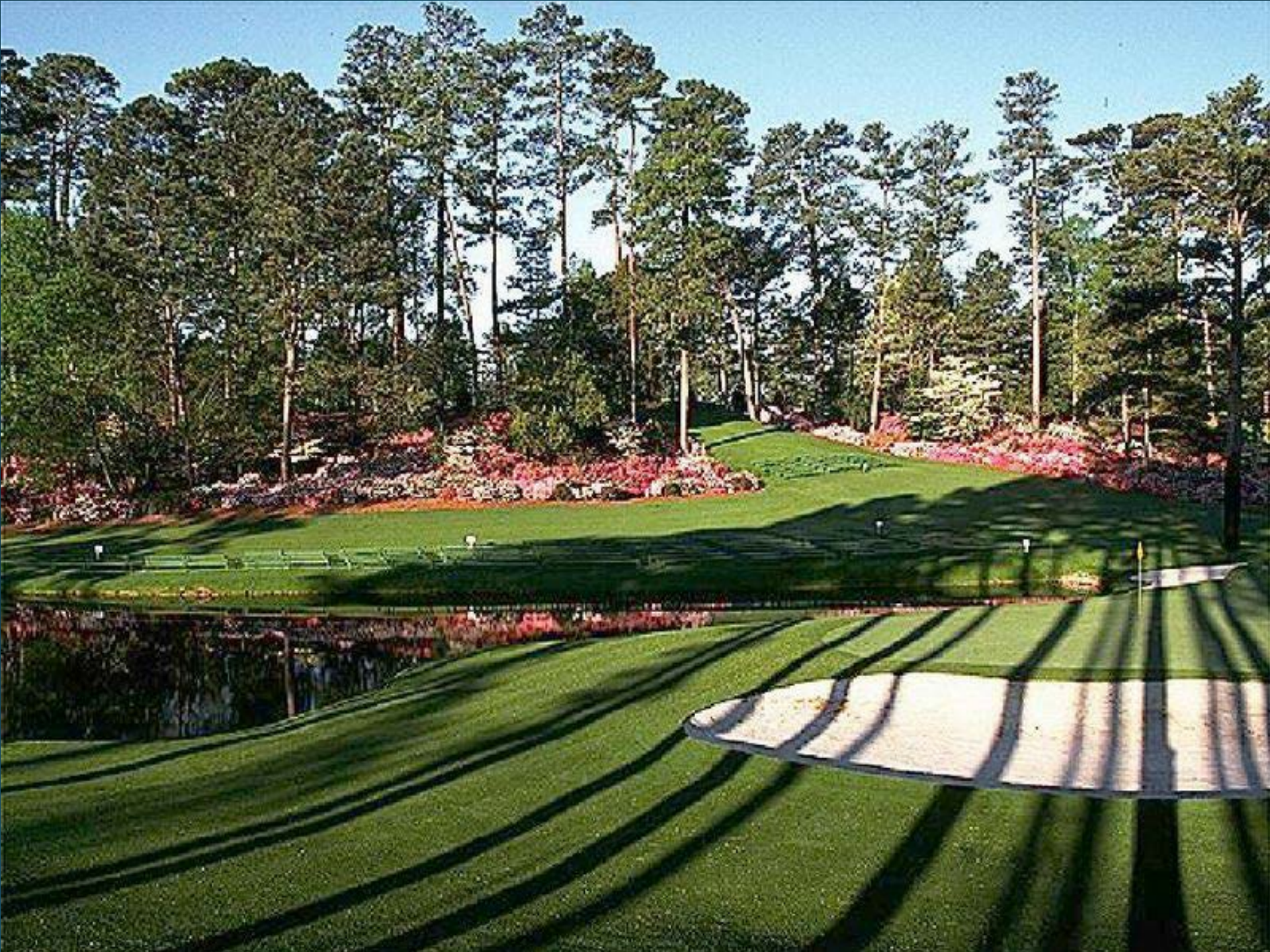
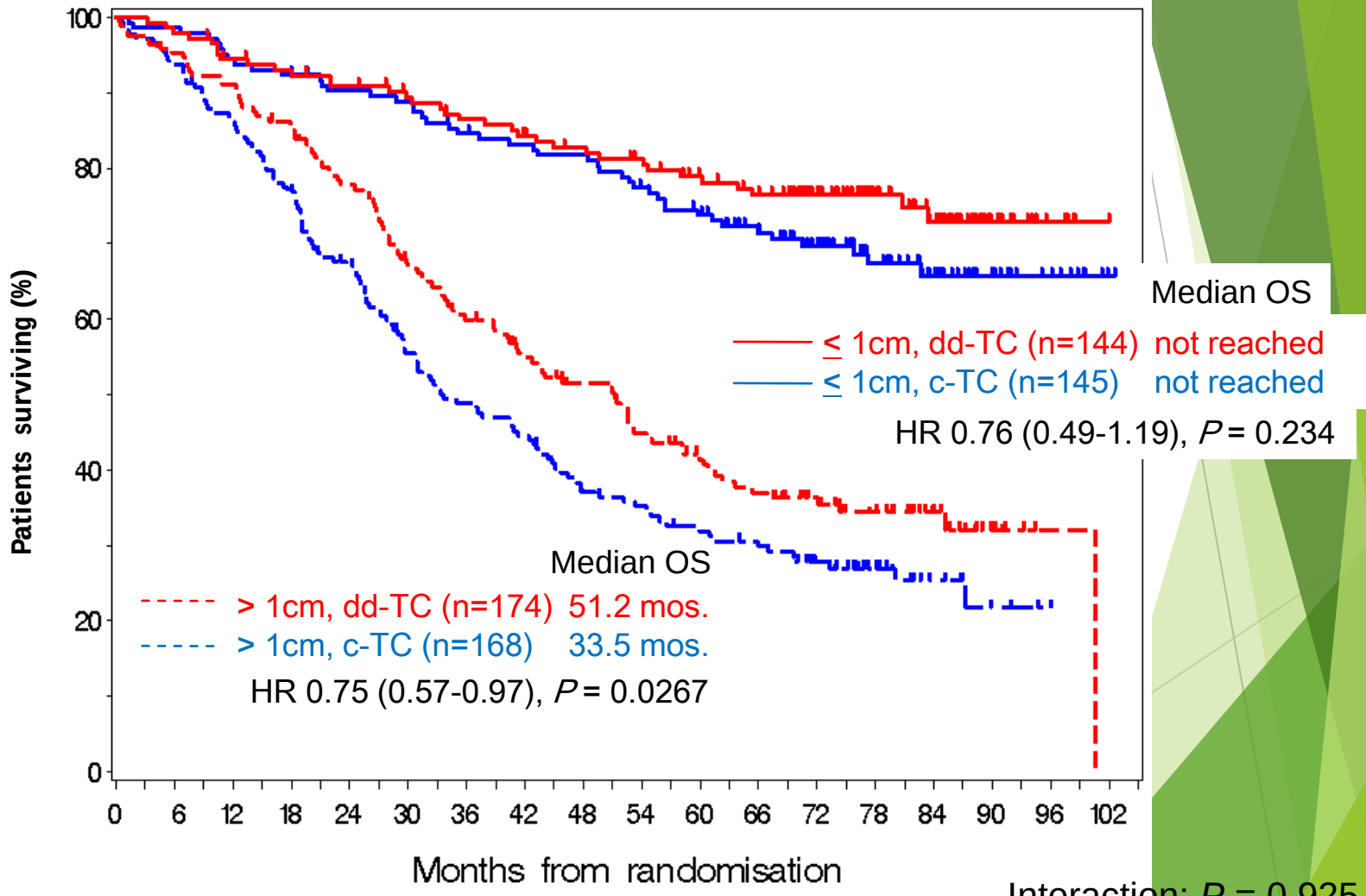


GOG 172 – NEJM 2006

- 429 pts with stage 3 ovarian or peritoneal cancer optimally debulked with residual disease less than 1.0 cm
- Randomized to paclitaxel i.v. @ 135 mg/m^2 on day 1 with either cisplatin i.v. @75 mg/m2 on day 2 or 100 mg/m^2 IP on day 2 and paclitaxel 60 mg/m^2 IP on day 8 q 21 days
- Median PFS 18.3 m versus 23.8 months for IP (p=0.05)
- Median OS 49.7 m versus 65.6 months for IP (p= 0.03)
- Only 42% of pts in IP arm completed 6 cycles
- Significantly higher global toxicity in IP arm (p < 0.001)
- QOL at one year identical in both arms

OS: by residual disease



Interaction: $P = 0.925$