Best of ASCO 2011

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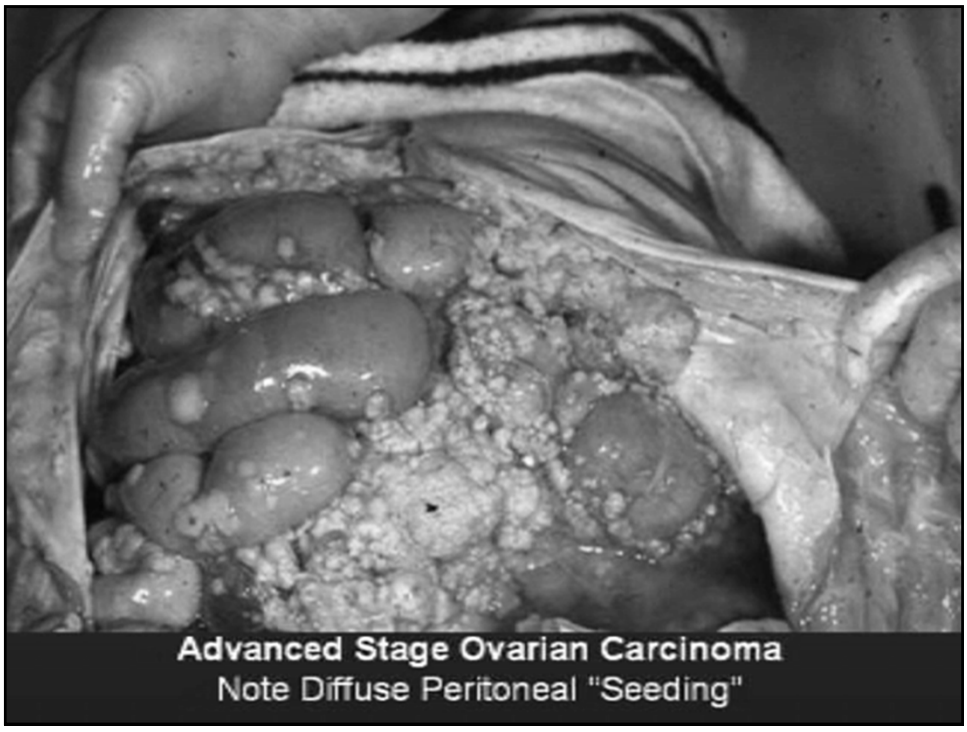
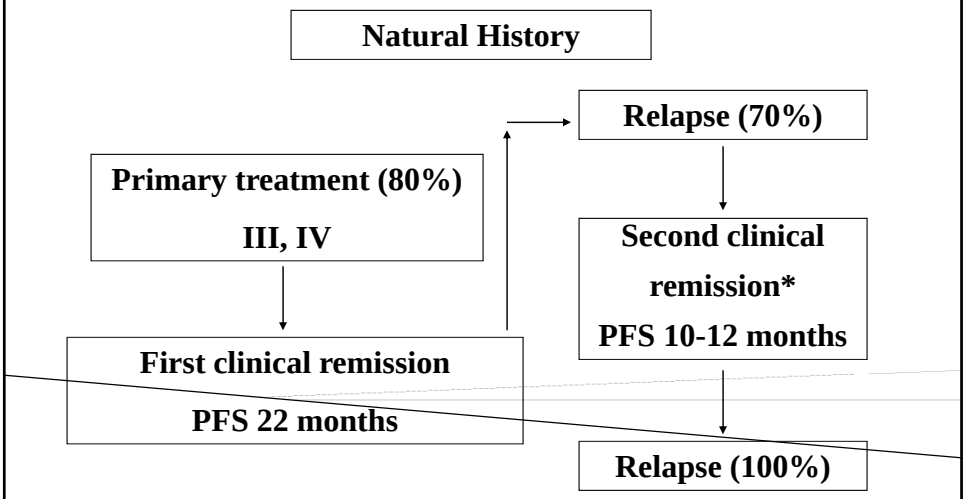
Ovarian Cancer

- In United States, Ovarian Cancer accounts for 4% of all newly diagnosed cancers in women
- 25,400 new cases every year
- Quite lethal , 4th most common cause of cancer deaths in women and 14,300 die annually
- Life time risk 1.4 (1.51 white, 0.91 black)
- 1 in 70 women in US will develop Ovarian Cancer, 1 in 100 will die from it.



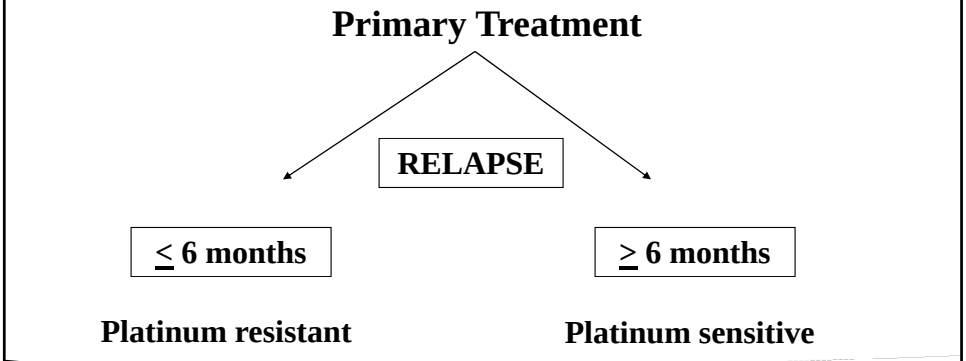
Advanced Stage Ovarian Carcinoma
Note Diffuse Peritoneal "Seeding"

Advanced Ovarian Cancer



Proc Am Soc Clin Oncol, 2001; abstr 838

Relapse Therapy: The Past



Recurrent Ovarian Cancer: defination of disease sensitivity

- Previous Treatment

time to recurrence : months

0 3 6 12 24 36

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refractory

resistant

sensitive

very sensitive

Platinum sensitive disease

- Disease Free Interval

Interval	Response
0-6 m	10 %
7-12 m	29 %
13-18 m	63 %
19-24 m	94 %

OCEANS, a phase III, multicenter, randomized, blinded, placebo-controlled trial of carboplatin and gemcitabine plus bevacizumab in patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer

C Aghajanian,[1] NJ Finkler,[2] T Rutherford,[3] MG Teneriello,[4] J Yi,[5] H Parmar,[5] MA Sovak,[5] LR Nycum[6]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Florida Hospital Gynecologic Oncology, Florida Hospital Cancer Institute, Orlando, FL; [3]Yale School of Medicine, New Haven, CT; [4]US Oncology, Texas Oncology, Austin, TX; [5]Genentech, Inc., South San Francisco, CA; [6]Forsyth Regional Cancer Center, Winston-Salem, NC, USA

OCEANS: Rationale

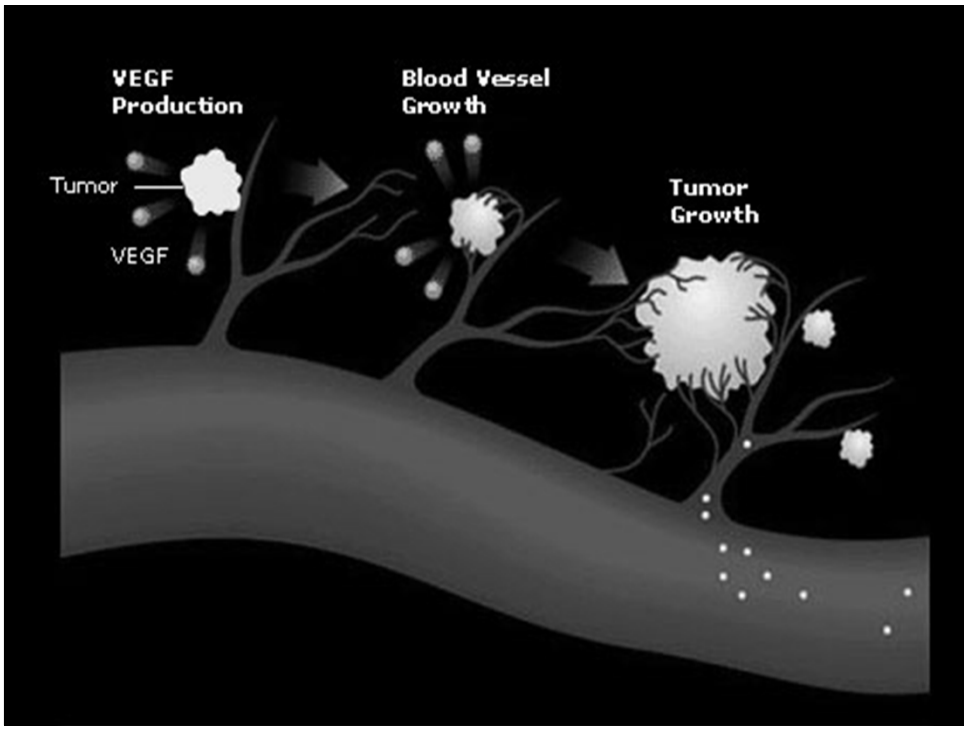
- Bevacizumab: single-agent activity in recurrent ovarian cancer (OC) (single-arm studies)[1,2]
- Carboplatin (C) + gemcitabine (G): phase III AGO/NCIC/EORTC trial in platinum-sensitive OC[3]

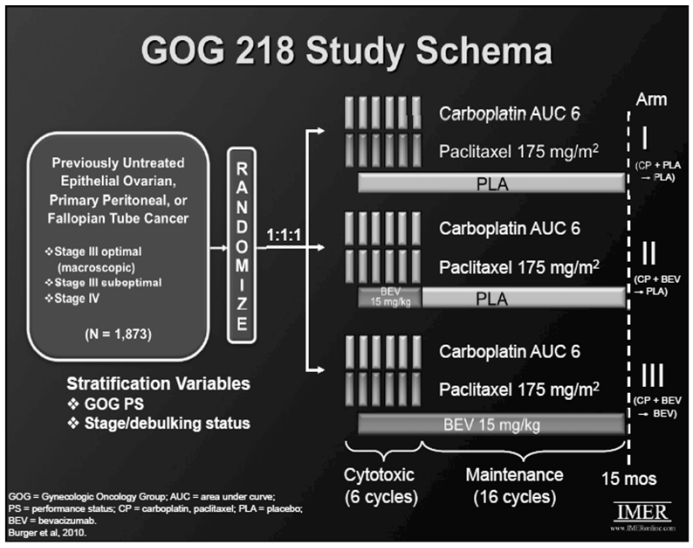
Efficacy	C (n=178)	CG (n=178)
Median PFS, months	5.8	8.6
HR for PFS	0.72 (p=0.0031)	
ORR, %	31	47
	p=0.0016	
Median OS, months	17.3	18.0
HR for OS	0.96 (p=0.7349)	

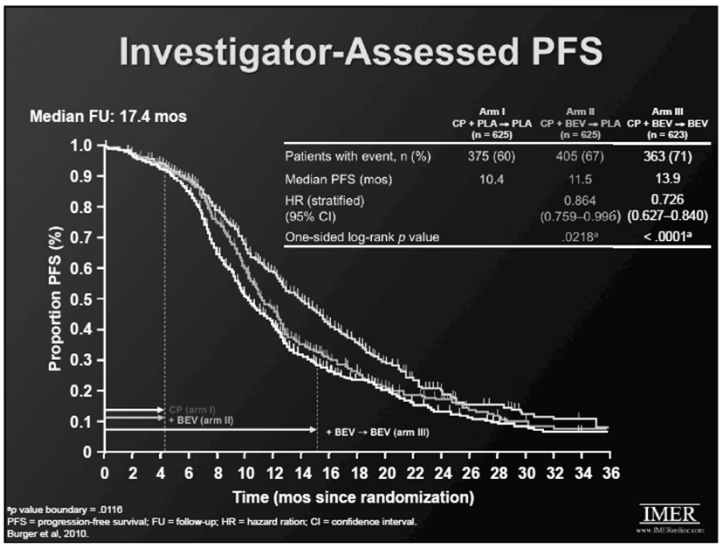
HR = hazard ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
[1]Burger et al. JCO 2007; [2]Cannistra et al. JCO 2007; [3]Pfisterer et al. JCO 2006

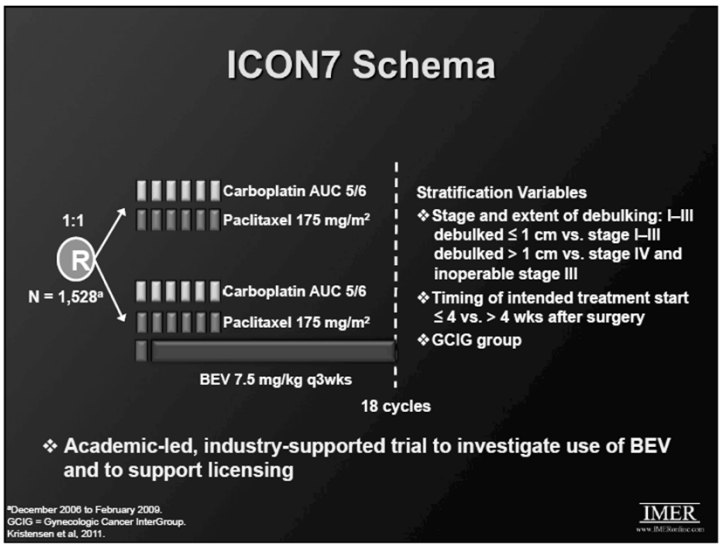
Bevacizumab in Ovarian Cancer

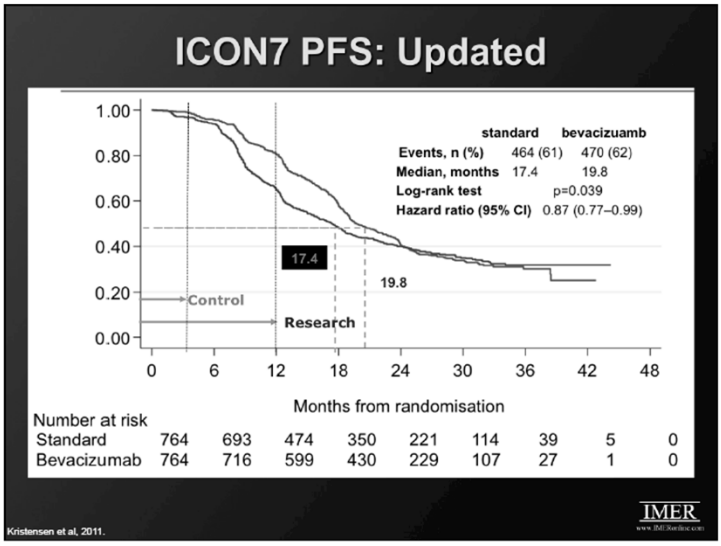
- Phase II GOG trial
- 64 pts, relapsed or progressive ovarian, primary peritoneal cancer with 1-2 prior regimens
- Bevacizumab at 15 mg/m2 q 3 weeks i.v.
- OR 17.7%, SD 54.8 %. Median duration of response 10.25 months, 38% of all pts with PFS > 6 months
- Grade 3-4 toxicity: Allergy (1), hypertension(5), GI(3), Pain(2), pulmonary (1)

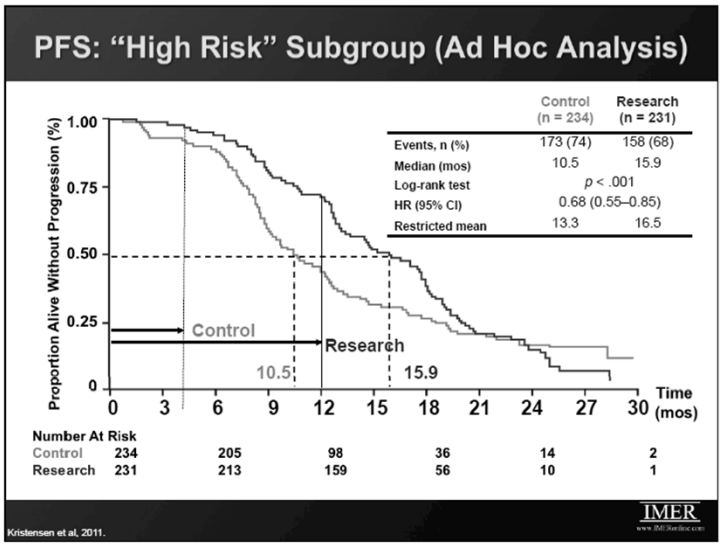


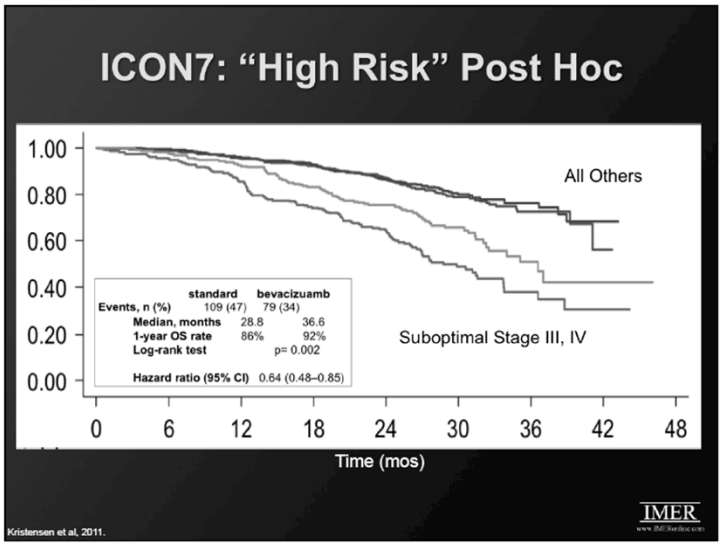

GOG 218 Study Schema
Previously Untreated Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Stage III optimal (macroscopic)
Stage III suboptimal
Stage IV
(N = 1,873)
RANDOMIZE
1:1:1
Stratification Variables
GOG PS
Stage/debulking status
Carboplatin AUC 6
Paclitaxel 175 mg/m²
PLA
Carboplatin AUC 6
Paclitaxel 175 mg/m²
BEV 15 mg/kg
PLA
Carboplatin AUC 6
Paclitaxel 175 mg/m²
BEV 15 mg/kg
Arm
I (CP + PLA → PLA)
II (CP + BEV → PLA)
III (CP + BEV → BEV)
Cytotoxic (6 cycles)
Maintenance (16 cycles)
15 mos
GOG = Gynecologic Oncology Group; AUC = area under curve; PS = performance status; CP = carboplatin, paclitaxel; PLA = placebo; BEV = bevacizumab.
Burger et al, 2010.
IMER


Investigator-Assessed PFS
Median FU: 17.4 mos
Arm I CP + PLA → PLA (n = 625)
Arm II CP + BEV → PLA (n = 625)
Arm III CP + BEV → BEV (n = 623)
Patients with event, n (%) 375 (60) 405 (67) 363 (71)
Median PFS (mos) 10.4 11.5 13.9
HR (stratified) (95% CI) 0.864 (0.759–0.996) 0.726 (0.627–0.840)
One-sided log-rank p value .0218a <.0001a
Proportion PFS (%)
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0
CP (arm I) + BEV (arm II)
+ BEV → BEV (arm III)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Time (mos since randomization)
ap value boundary = .0116
PFS = progression-free survival; FU = follow-up; HR = hazard ration; CI = confidence interval.
Burger et al, 2010.
IMER


ICON7 Schema
1:1
R
N = 1,528[a]
Carboplatin AUC 5/6
Paclitaxel 175 mg/m²
Carboplatin AUC 5/6
Paclitaxel 175 mg/m²
BEV 7.5 mg/kg q3wks
18 cycles
Stratification Variables
❖Stage and extent of debulking: I–III debulked ≤ 1 cm vs. stage I–III debulked > 1 cm vs. stage IV and inoperable stage III
❖Timing of intended treatment start ≤ 4 vs. > 4 wks after surgery
❖GCIG group
❖ Academic-led, industry-supported trial to investigate use of BEV and to support licensing
[a]December 2006 to February 2009.
GCIG = Gynecologic Cancer InterGroup.
Kristensen et al, 2011.
IMER


ICON7 PFS: Updated
1.00
0.80
0.60
0.40
0.20
0.00
standard bevacizuamb
Events, n (%) 464 (61) 470 (62)
Median, months 17.4 19.8
Log-rank test p=0.039
Hazard ratio (95% CI) 0.87 (0.77–0.99)
17.4
19.8
Control
Research
0 6 12 18 24 30 36 42 48
Months from randomisation
Number at risk
Standard 764 693 474 350 221 114 39 5 0
Bevacizumab 764 716 599 430 229 107 27 1 0
Kristensen et al, 2011.
IMER


PFS: "High Risk" Subgroup (Ad Hoc Analysis)
Control (n = 234)
Research (n = 231)
Events, n (%) 173 (74) 158 (68)
Median (mos) 10.5 15.9
Log-rank test p < .001
HR (95% CI) 0.68 (0.55–0.85)
Restricted mean 13.3 16.5
Proportion Alive Without Progression (%)
1.00
0.75
0.50
0.25
0
Control
Research
10.5
15.9
0 3 6 9 12 15 18 21 24 27 30
Time (mos)
Number At Risk
Control 234 205 98 36 14 2
Research 231 213 159 56 10 1
Kristensen et al, 2011.
IMER


ICON7: "High Risk" Post Hoc
1.00
0.80
0.60
0.40
0.20
0.00
All Others
Suboptimal Stage III, IV
standard bevacizuamb
Events, n (%) 109 (47) 79 (34)
Median, months 28.8 36.6
1-year OS rate 86% 92%
Log-rank test p= 0.002
Hazard ratio (95% CI) 0.64 (0.48–0.85)
0 6 12 18 24 30 36 42 48
Time (mos)
Kristensen et al, 2011.
IMER

OCEANS: Rationale

- Bevacizumab: single-agent activity in recurrent ovarian cancer (OC) (single-arm studies)[1,2]
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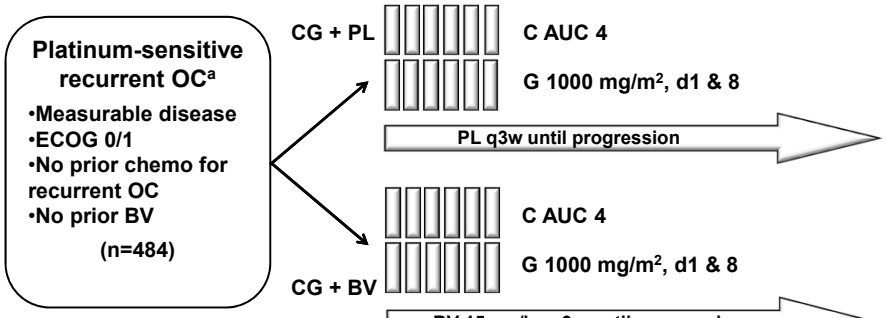
OCEANS: Study schema



Stratification variables:

- Platinum-free interval (6–12 vs >12 months)
- Cytoreductive surgery for recurrent disease (yes vs no)

BV = bevacizumab; PL = placebo
[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer

OCEANS: Statistical design

- Primary endpoint: PFS by RECIST (investigator assessed)
- Secondary endpoints: ORR, duration of response, OS, safety
- PFS also assessed by Independent Review Committee (IRC)
- Planned sample size: 480
- Median PFS: 8.6 months → 11.8 months
  - 80% power; HR 0.73; 317 events; α =0.05
- Median OS: 18.0 months → 22.8 months
  - 60% power; HR 0.79; 353 events
  - Interim OS at time of PFS analysis; α =0.001
  - Final OS will be tested at α =0.049

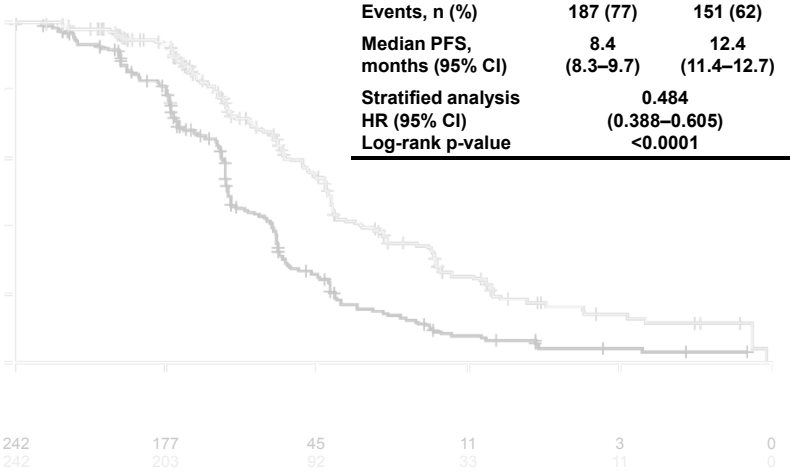
OCEANS: Patient characteristics

Characteristic	CG + PL (n=242)	CG + BV (n=242)
Median age, years (range)	61 (28−86)	60 (38–87)
Age ≥65 years, %	38	35
Race, %		
White	92	90
Other	8	10
ECOG PS 0, %	76	75
Histologic subtype, %		
Serous	84	78
Mucinous/clear cell	3	5
Other	14	17
Platinum-free interval, %		
6–12 months	42	41
>12 months	58	59
Cytoreductive surgery for recurrent disease, %	10	12

OCEANS: Treatment exposure

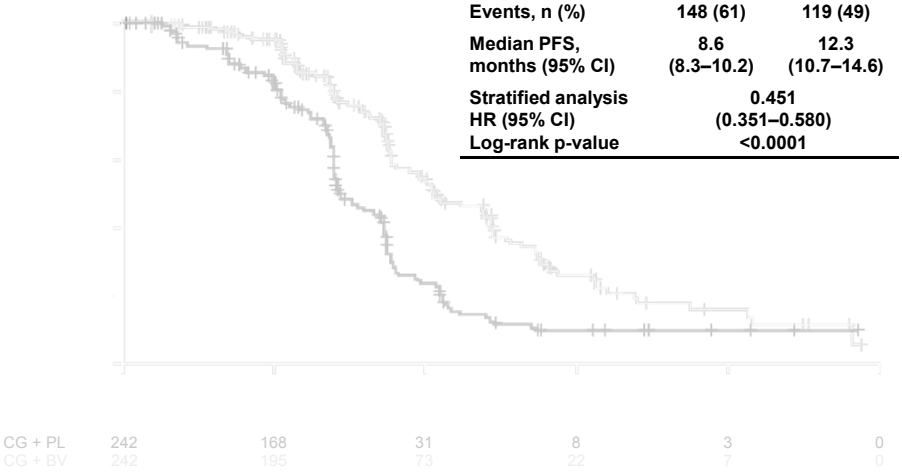
Treatment delivered	CG + PL (n=233)	CG + BV (n=247)
Chemotherapy		
Median No. of cycles (range)	6 (1–10)	6 (1–10)
Patients receiving 7–10 cycles, %		
Carboplatin	40	33
Gemcitabine	46	41
Bevacizumab/placebo		
Median No. of cycles (range)	10 (1–36)	12 (1–43)

OCEANS: Primary analysis of PFS



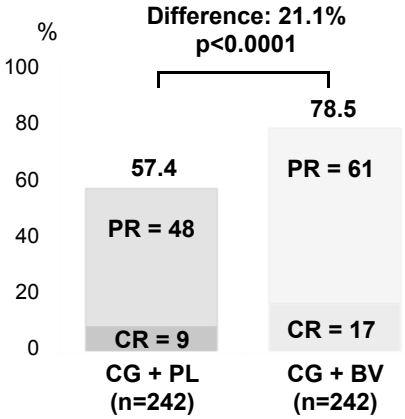
	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI)	0.484 (0.388–0.605)	
Log-rank p-value	<0.0001	

OCEANS: PFS by IRC



	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	148 (61)	119 (49)
Median PFS, months (95% CI)	8.6 (8.3–10.2)	12.3 (10.7–14.6)
Stratified analysis HR (95% CI)	0.451 (0.351–0.580)	
Log-rank p-value	<0.0001	

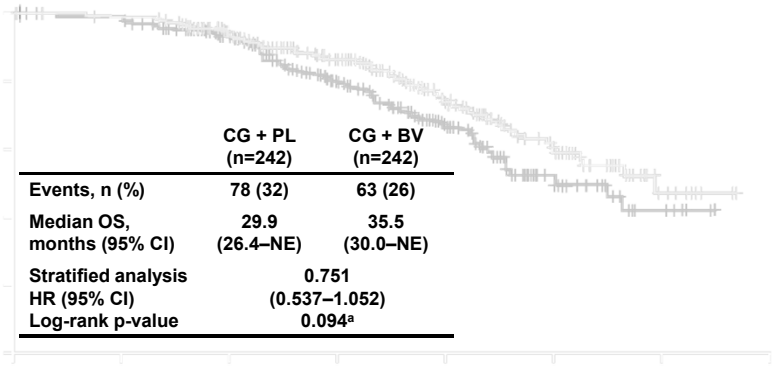
OCEANS: Objective response



Duration of response	CG + PL (n=139)	CG + BV (n=190)
Median, months	7.4	10.4
HR (95% CI)	0.534 (0.408–0.698)	
	p<0.0001[a]	

[a]Compared for descriptive purposes only

OCEANS: Interim OS



	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	78 (32)	63 (26)
Median OS, months (95% CI)	29.9 (26.4–NE)	35.5 (30.0–NE)
Stratified analysis HR (95% CI)	0.751 (0.537–1.052)	
Log-rank p-value	0.094[a]	

CG + PL	242	235	195	131	77	26	8	0
CG + BV	242	238	200	146	82	42	8	0

NE = not estimable
[a]p-value does not cross pre-specified boundary of 0.001

OCEANS: Overview of AEs

Patients, %	CG + PL (n=233)	CG + BV (n=247)
Any AE	100	100
Serious AE	25	35
Grade 3–5 AE	82	90
Grade 3–5 AE of special interest	62	74
Grade 5 AE	<1[a]	<1[b]

[a]Acute myocardial infarction in one patient
[b]Intracranial hemorrhage in one patient

OCEANS: AEs of special interest

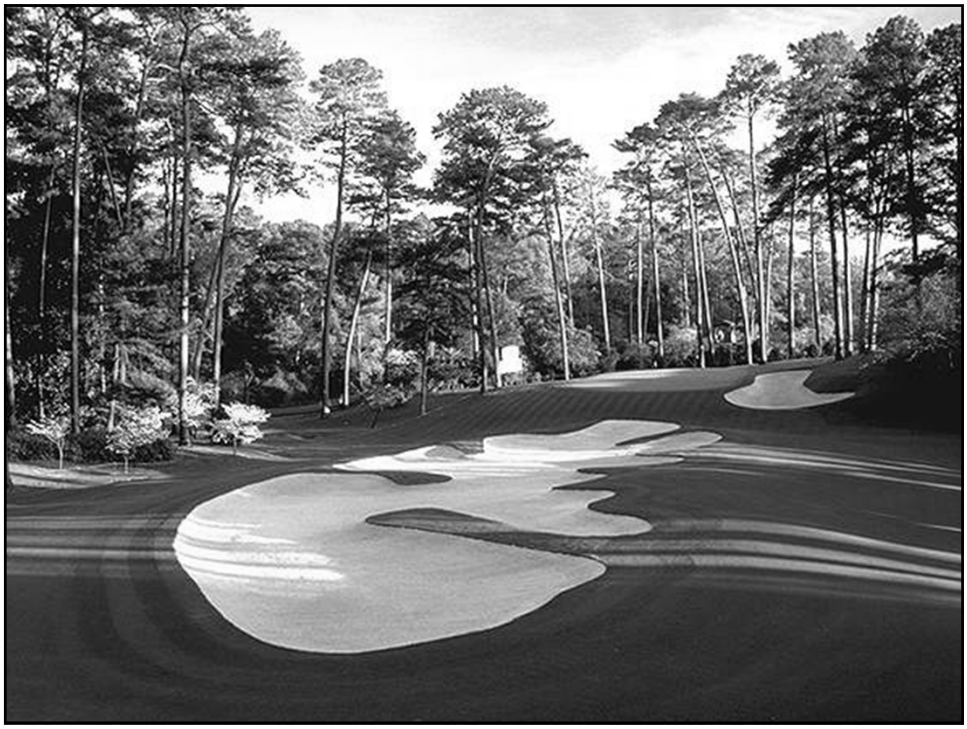
Patients, %	CG + PL (n=233)	CG + BV (n=247)
ATE, all grades	1	3
VTE, grade ≥3	3	4
CNS bleeding, all grades	<1	1
Non-CNS bleeding, grades ≥3	1	6
CHF, grades ≥3	1	1
Neutropenia, grade ≥3	56	58
Febrile neutropenia, grade ≥3	2	2
Hypertension, grade ≥3	<1	17
Fistula/abscess, all grades	<1	2
GI perforation, all grades	0	0[a]
Proteinuria, grade ≥3	1	9
RPLS, all grade	0	1
Wound-healing complication, grades ≥3	0	1

ATE = arterial thromboembolic event; CHF = congestive heart failure; GI = gastrointestinal; RPLS = reversible posterior leukoencephalopathy syndrome; VTE = venous thromboembolic event
[a]Two GI perforations occurred 69 days after last BV dose

OCEANS: Conclusions

- Bevacizumab + carboplatin + gemcitabine followed by bevacizumab until progression provides a clinically meaningful benefit over chemotherapy alone in recurrent OC
  - Improved PFS: HR 0.484 ($p<0.0001$); median 8.4 → 12.4 months
  - Improved ORR and duration of response
  - OS data not yet mature
- Safety data consistent with bevacizumab profile
  - No GI perforations and no new safety signals

This regimen should be considered a new option for recurrent platinum-sensitive OC

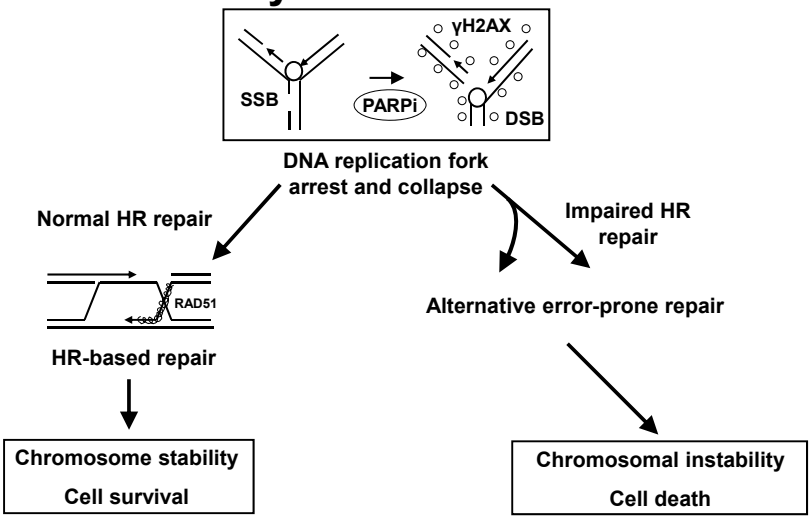


Phase II randomized placebo-controlled study of olaparib in patients with platinum-sensitive relapsed serous ovarian cancer

Jonathan Ledermann,[1] P Harter,[2] C Gourley,[3] M Friedlander,[4] I Vergote,[5] G Rustin,[6] C Scott,[7] W Meier,[8] R Shapira Frommer,[9] T Safra,[10] D Matei,[11] E Macpherson,[12] C Watkins,[12] J Carmichael,[12] U Matulonis[13]

[1]University College London, London, UK; [2]Kliniken Essen Mitte, Essen, Germany; [3]University of Edinburgh Cancer Research UK Centre, Edinburgh, UK; [4]Prince of Wales Hospital, Randwick, Australia; [5]University of Leuven, Leuven, European Union; [6]Mount Vernon Hospital, Northwood, UK; [7]Royal Melbourne Hospital, Parkville, Australia; [8]Evangelical Hospital, Düsseldorf, Germany; [9]Chaim Sheba Medical Center, Tel Hashomer, Israel; [10]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [11]Indiana University School of Medicine, Indianapolis, USA; [12]AstraZeneca, Macclesfield, UK; [13]Dana-Farber Cancer Institute, Boston, USA

PARP inhibition and tumor-selective synthetic lethality



HR, homologous recombination; SSB, single-strand break; DSB, double-strand break
Farmer H *et al. Nature* 2005;434:917–921; Bryant HE *et al. Nature* 2005;434:913–917

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Homologous recombination repair deficiency in ovarian cancer

- 10–15% of epithelial ovarian cancers are deficient in homologous recombination repair due to *BRCA1* or *BRCA2* mutations[1]
- Up to 50% of high-grade serous ovarian cancer patients could be deficient in homologous recombination repair because of:[2]
  - Germ-line or somatically acquired *BRCA1* or *BRCA2* mutations
  - Epigenetic inactivation of *BRCA1*
  - *BRCA1/BRCA2*-independent defects in the homologous recombination pathway

1. Bast Jr, RC *et al. Nat Rev Oncol* 2009;9:415–428; 2. Press JZ *et al. BMC Cancer* 2008;8:17

Olaparib: An orally active PARP inhibitor

	Olaparib Phase I and *BRCA* mutation expansion studies[1]
Olaparib dose	200 mg bid
RECIST CR/PR	28%
Disease control rate*	34%
Median duration of response	7.0 months

***Complete response (CR) + partial response (PR) + stable disease (SD); NR, not reported**

1. Fong PC *et al. J Clin Oncol* 2010;28:2512–2519; 2. Audeh MW *et al. Lancet* 2010;376:245–251;
3. Gelmon KA *et al. J Clin Oncol* 2010;28:abst 3002

Olaparib: An orally active PARP inhibitor

	Olaparib Phase I and *BRCA* mutation expansion studies[1]	Olaparib multicenter Phase II *BRCA* mutation ovarian cancer study[2]
Olaparib dose	200 mg bid	400 mg bid
RECIST CR/PR	28%	33%
Disease control rate*	34%	69%
Median duration of response	7.0 months	9.5 months

***Complete response (CR) + partial response (PR) + stable disease (SD); NR, not reported**

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Olaparib dose	200 mg bid	400 mg bid	400 mg bid
RECIST CR/PR	28%	33%	*BRCA*+ 41% *BRCA*- 24%
Disease control rate*	34%	69%	*BRCA*+ 76% *BRCA*- 62%
Median duration of response	7.0 months	9.5 months	NR

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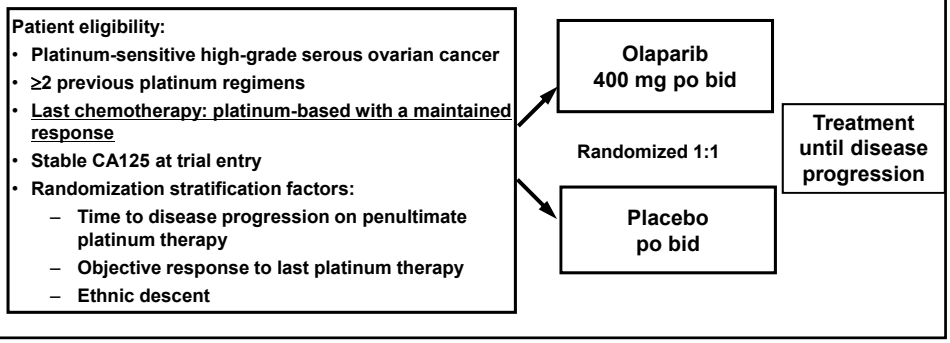
***Complete response (CR) + partial response (PR) + stable disease (SD); NR, not reported**

Provides clinical evidence of activity in patients with and without *BRCA1/2* mutations

1. Fong PC *et al. J Clin Oncol* 2010;28:2512–2519; 2. Audeh MW *et al. Lancet* 2010;376:245–251;
3. Gelmon KA *et al. J Clin Oncol* 2010;28:abst 3002

Study aim and design

- To assess the efficacy of oral olaparib as a maintenance treatment in patients with platinum-sensitive high-grade serous ovarian cancer
- Randomized, double-blind, placebo-controlled Phase II study
- Multinational study; 82 sites in 16 countries



Study endpoints

Primary endpoint:

- Progression-free survival by RECIST*

Secondary endpoints included:

- Time to progression by CA125 (GCIG criteria) or RECIST
- Overall survival
- Objective response rate by RECIST
- Health-related quality of life
- Safety and tolerability

*Measured from randomization upon completion of chemotherapy

Statistical considerations

- 250 patients were planned for recruitment
  - Actual recruitment: 265 patients randomized
- Primary analysis of PFS used Cox proportional hazards*
- To be performed following ≥137 PFS events
  - Size based on detecting an increased median PFS from **9 to 12** months (hazard ratio = 0.75)
- 80% power to demonstrate a promising treatment effect i.e. *P*< 0.2, 1-sided

***With covariates for the randomization stratification factors**

Patient characteristics

	Olaparib 400 mg bid (n=136)	**Placebo (n=129)**
Median age, years (range)	58 (21–89)	59 (33–84)
Ethnicity, n (%)		
Jewish descent	20 (15)	17 (13)
ECOG status, n		
0 / 1 / 2 / unknown	110 / 23 / 1 / 2	95 / 30 / 2 / 2
BRCA mutation status, n (%)*		
BRCA1	25 (18)	20 (16)
BRCA2	6 (4)	7 (5)
BRCA1 & BRCA2	0	1 (1)
Known negative	18 (13)	20 (16)
Unknown	87 (64)	81 (63)

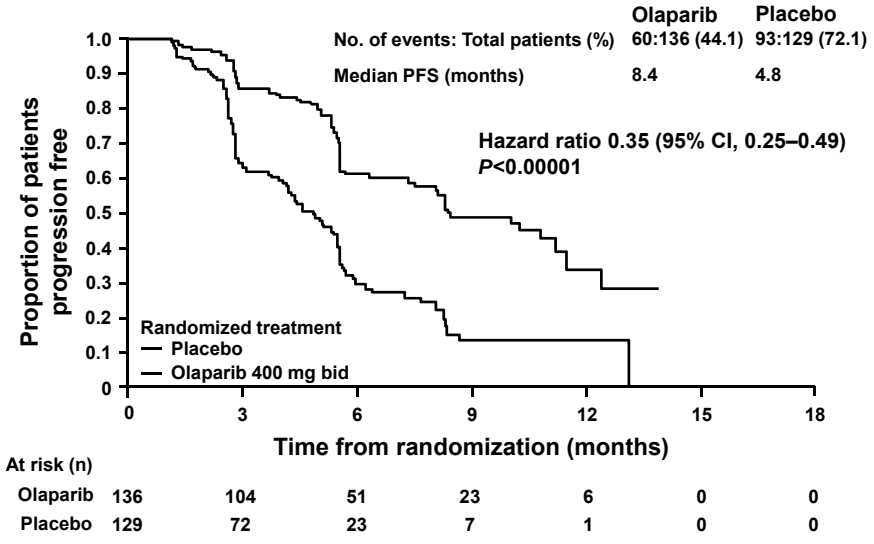
***BRCA mutation status was not a requirement**

Patient characteristics (continued)

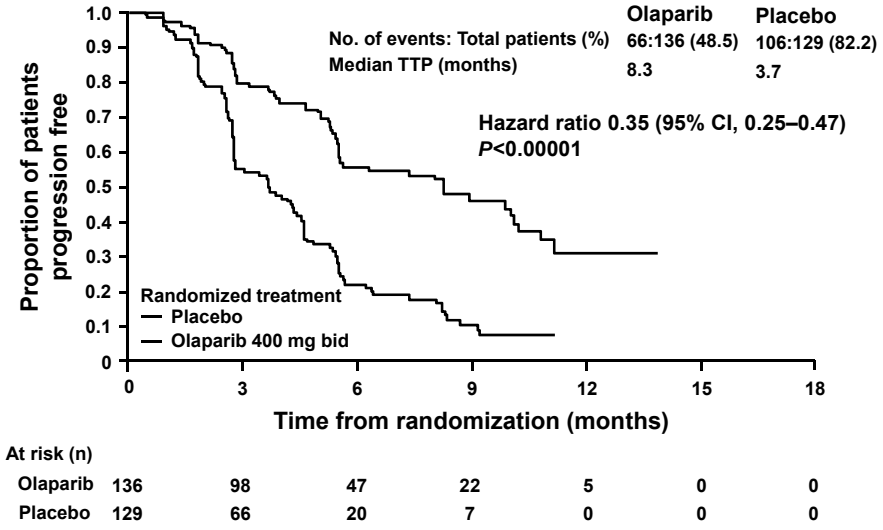
	Olaparib 400 mg bid (n=136)	Placebo (n=129)
TTP on penultimate platinum regimen, n (%)		
>6–12 months	53 (39)	54 (42)
>12 months	83 (61)	75 (58)
Objective response to last platinum, n (%)		
CR	57 (42)	63 (48)
PR	79 (58)	66 (51)
Prior chemotherapy regimens		
Median (range)	3 (0–11)*	3 (2–8)
Prior platinum-containing chemotherapy regimens		
Median (range)	2 (0–7)*	2 (2–8)
Time from completion of final platinum chemotherapy to randomization, days		
Median (range)	39 (15–517)	41 (14–70)

*One patient had two regimens of platinum-based therapy which were not recorded as the data were not entered into the database prior to database lock; this patient is therefore classed as having zero chemotherapy regimens. TTP, time to progression

Progression-free survival



Time to progression by CA125 (GCIG) or RECIST



At risk (n)							
Olaparib	136	98	47	22	5	0	0
Placebo	129	66	20	7	0	0	0

Further secondary endpoints

- Overall survival data immature
  - At the time of PFS analysis, 19/265 deaths:
    - 9 in olaparib 400 mg bid group
    - 10 in placebo group
  - Overall survival follow-up is ongoing
- Objective response rate by RECIST
  - 7/57 (12.3%) PR in olaparib 400 mg bid group
  - 2/48 (4.2%) PR placebo group
- Disease control rate: no evidence of progression at 24 weeks
  - 72/136 (53%) in olaparib 400 mg bid group
  - 32/129 (25%) in placebo group

Health-related quality of life

- No statistically significant differences in improvement rates for HRQoL measures (TOI, FACT-O, FOSI) between treatment arms (2-sided *P*>0.05)
- No statistically significant difference in time to worsening of HRQoL measures
  - Numerically shorter for olaparib versus placebo

FACT-O, functional assessment of cancer therapy – ovarian cancer; FOSI, FACT/NCCN ovarian symptom index; TOI, trial outcome index

Common Adverse Events*

	Olaparib 400 mg bid (n=136)		Placebo (n=128)	
	Percentage of Patients			
Adverse event	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any event	61	35	70	20
Nausea	66	2	35	0
Fatigue	42	7	34	3
Vomiting	29	2	13	1
Diarrhea	21	2	20	2
Headache	18	0	11	1
Decreased appetite	18	0	13	0
Abdominal pain	16	2	23	3
Anemia	12	5	4	1
Dyspepsia	16	0	9	0

*Adverse events graded according to maximum CTCAE version 3.0 grade, experienced by >15% of patients in either treatment group.

Common Adverse Events*

	Olaparib 400 mg bid (n=136)		Placebo (n=128)	
	Percentage of Patients			
Adverse event	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any event	61	35	70	20
Nausea	66	2	35	0
Fatigue	42	7	34	3
Vomiting	29	2	13	1
Diarrhea	21	2	20	2
Headache	18	0	11	1
Decreased appetite	18	0	13	0
Abdominal pain	16	2	23	3
Anemia	12	5	4	1
Dyspepsia	16	0	9	0

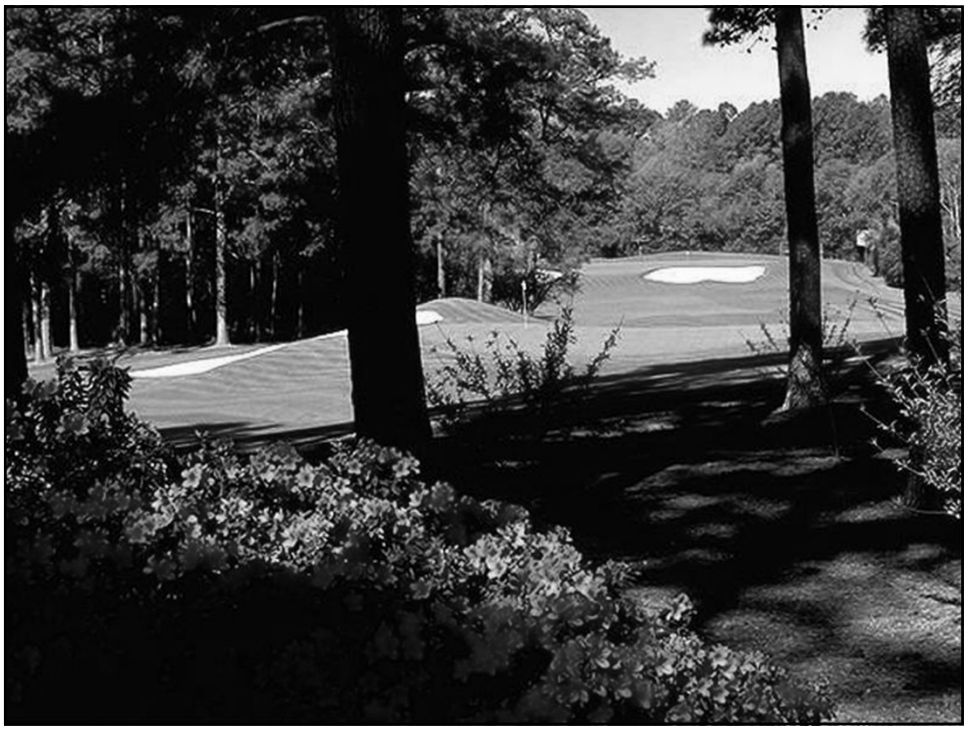
*Adverse events graded according to maximum CTCAE version 3.0 grade, experienced by >15% of patients in either treatment group.

Dose adjustments, discontinuations and treatment duration

	Olaparib 400 mg bid (n=136)	Placebo (n=128)
Discontinuations due to AEs, n (%)	3 (2)	1 (1)
Dose interruptions due to AEs, n (%)	41 (30)	12 (9)
Dose reductions due to AEs, n (%)	26 (19)	3 (2)
Median treatment duration, days	207	141

Conclusions

- First study demonstrating a significant PFS benefit following maintenance treatment with a PARP inhibitor for platinum-sensitive relapsed serous ovarian cancer
- Olaparib improved median PFS by 3.6 months compared with placebo, following completion of chemotherapy
- Olaparib was generally well tolerated
- 50% of olaparib and 16% of placebo patients were still on treatment at the time of the analysis
- Further studies will be needed to determine the role of olaparib in the management of serous ovarian cancer

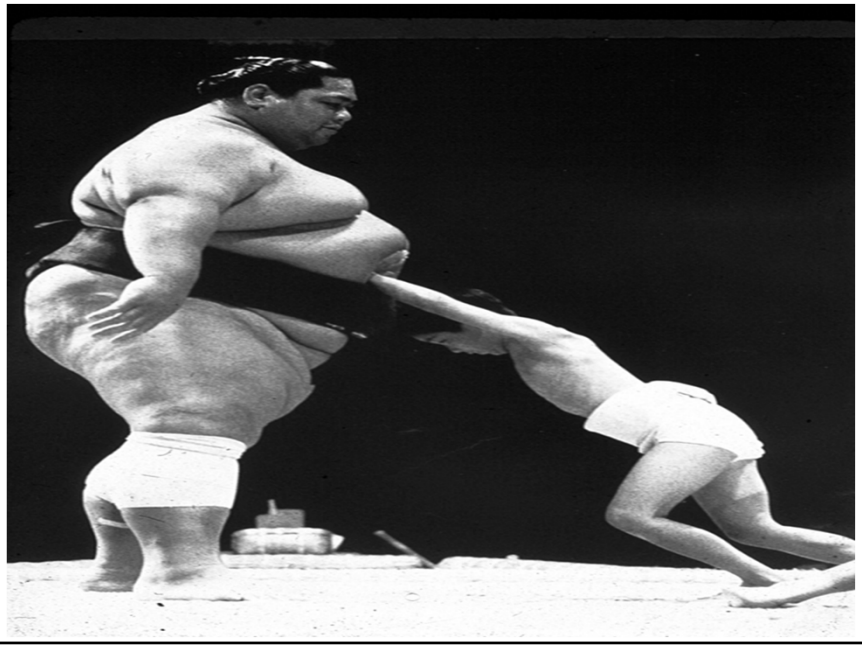


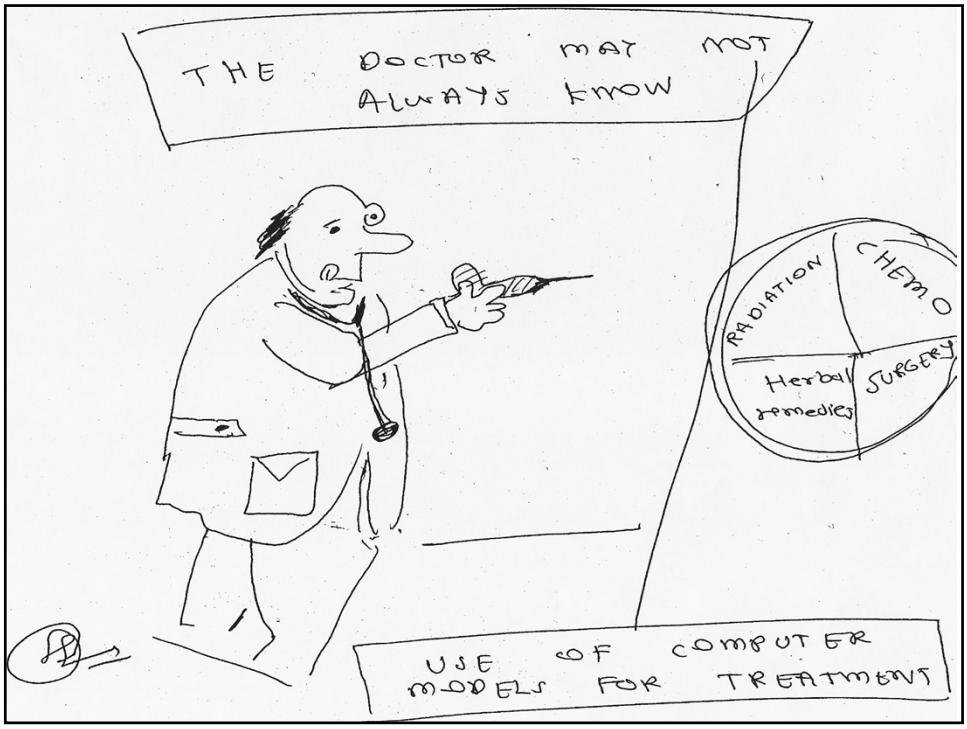
PRECEDENT: A randomized phase II trial comparing EC145 and pegylated liposomal doxorubicin (PLD) in combination, versus PLD alone, in subjects with platinum-resistant ovarian cancer.

R. W. Naumann, R. L. Coleman, R. A. Burger, T. J. Herzog, R. Morris, E. A. Sausville, E. Kutarska, S. A. Ghamande, N. Y. Gabrail, S. De Pasquale, E. Nowara, L. Gilbert, J. R. Caton, R. H. Gersh, M. G. Teneriello, W. A. Harb, P. Konstantinopoulos, J. T. Symanowski, C. Lovejoy, R. A. Messmann;

Blumenthal Cancer Center Carolinas Medical Center, Charlotte, NC; University of Texas M. D. Anderson Cancer Center, Houston, TX; Fox Chase Cancer Center, Philadelphia, PA; Columbia University Cancer Center, New York, NY; Karmanos Cancer Institute/Wayne State University, Detroit, MI; University of Maryland School of Medicine and University of Maryland Greenebaum Cancer Center, Baltimore, MD; Centrum Onkologii Ziemi Lubelskiej, Lublin, Poland; Medical College of Georgia, Augusta, GA; Gabrail Cancer Center, Canton, OH; Chattanooga's Program in Women's Oncology, Chattanooga, TN; Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland; McGill University Health Centre, Montreal, QC, Canada; Willamette Valley Cancer Center, Eugene, OR; Cancer Center of Northwest, Spokane, WA; US Oncology, The Woodlands, TX; Horizon Oncology Center, Lafayette, IN; Beth Israel Deaconess Medical Center, Boston, MA; Nevada Cancer Institute, Las Vegas, NV; Endocyte, Inc., West Lafayette, IN

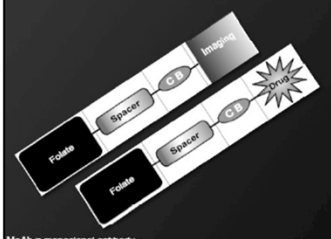
Platinum Resistant Ovarian Cancer

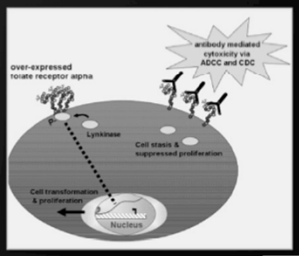




Utilizing the Folate Receptor

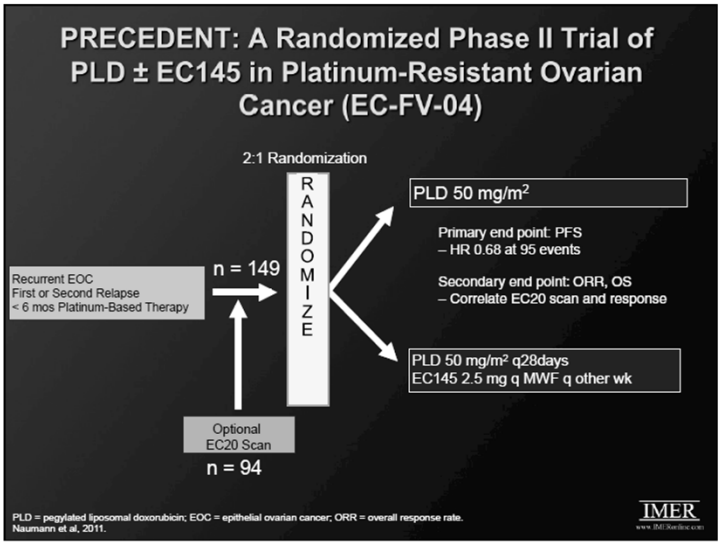
- EC145
  - Folate-vinca conjugate
  - Relevant for imaging targeting and therapy
- Farletuzumab
  - Humanized MoAb

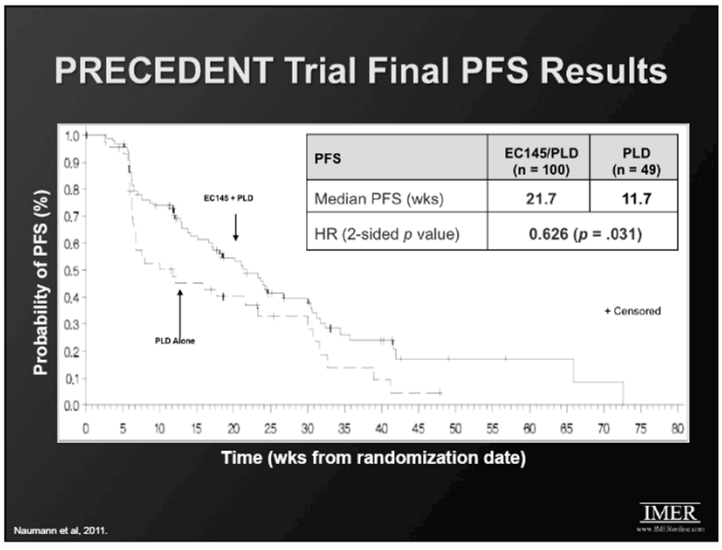


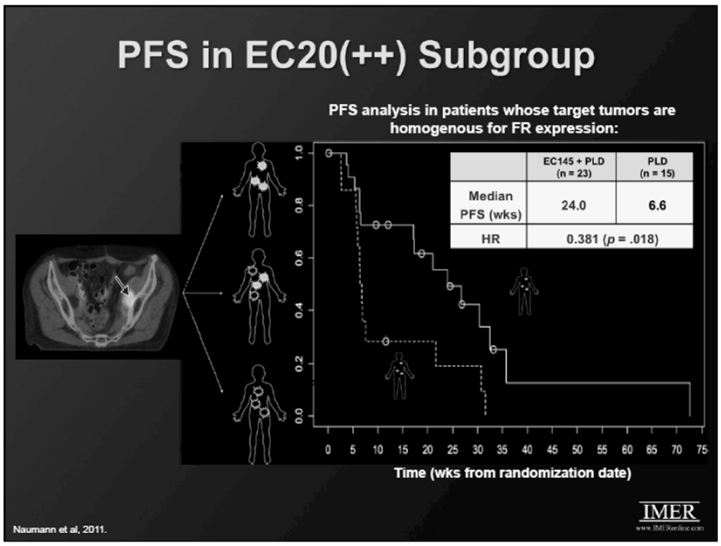


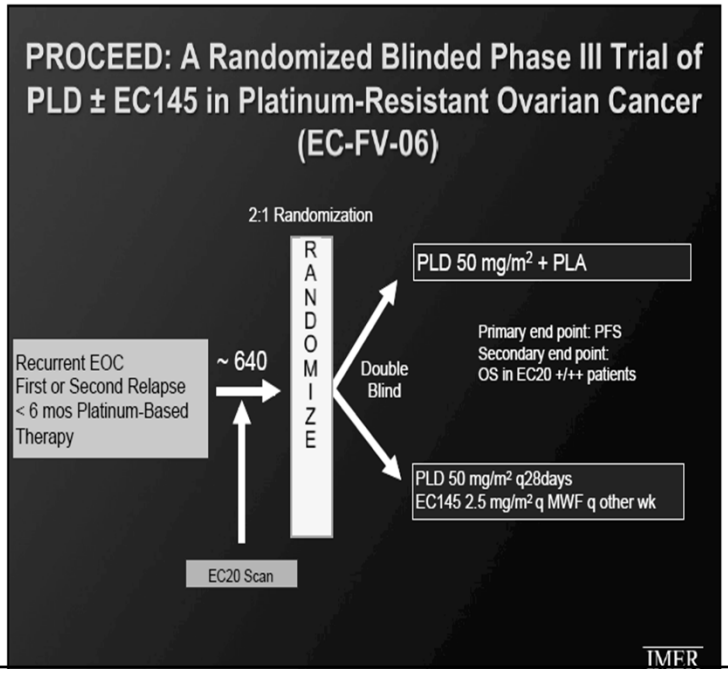
MoAb = monoclonal antibody.
Konner et al, 2010; Dosio et al, 2010; Spannuth et al, 2010.

IMER


PRECEDENT: A Randomized Phase II Trial of PLD ± EC145 in Platinum-Resistant Ovarian Cancer (EC-FV-04)
2:1 Randomization
Recurrent EOC
First or Second Relapse
< 6 mos Platinum-Based Therapy
n = 149
RANDOMIZE
PLD 50 mg/m²
Primary end point: PFS
– HR 0.68 at 95 events
Secondary end point: ORR, OS
– Correlate EC20 scan and response
PLD 50 mg/m² q28days
EC145 2.5 mg q MWF q other wk
Optional
EC20 Scan
n = 94
PLD = pegylated liposomal doxorubicin; EOC = epithelial ovarian cancer; ORR = overall response rate.
Naumann et al, 2011.
IMER


PRECEDENT Trial Final PFS Results
Probability of PFS (%)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
EC145 + PLD
PLD Alone
+ Censored
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80
Time (wks from randomization date)
PFS | EC145/PLD (n = 100) | PLD (n = 49)
Median PFS (wks) | 21.7 | 11.7
HR (2-sided p value) | 0.626 (p = .031)
Naumann et al, 2011.
IMER


PFS in EC20(++) Subgroup
PFS analysis in patients whose target tumors are homogenous for FR expression:
EC145 + PLD (n = 23)
PLD (n = 15)
Median PFS (wks)
24.0
6.6
HR
0.381 (p = .018)
0.0
0.2
0.4
0.6
0.8
1.0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Time (wks from randomization date)
Naumann et al, 2011.
IMER


PROCEED: A Randomized Blinded Phase III Trial of PLD ± EC145 in Platinum-Resistant Ovarian Cancer (EC-FV-06)
2:1 Randomization
Recurrent EOC
First or Second Relapse
< 6 mos Platinum-Based Therapy
~ 640
EC20 Scan
RANDOMIZE
Double Blind
PLD 50 mg/m² + PLA
PLD 50 mg/m² q28days
EC145 2.5 mg/m² q MWF q other wk
Primary end point: PFS
Secondary end point:
OS in EC20 +/++ patients
IMER

Effect of Screening on Ovarian Cancer Mortality

Results of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Randomized Screening Trial

SS Buys, E Partridge, A Black, CC Johnson, L Lamerato, C Isaacs, DJ Reding, RT Greenlee, B Kessel, MN Fouad, D Chia, L Ragard, J Rathmell, P Hartge, PF Pinsky, G Izmirlian, J-L Xu, PC Prorok, CD Berg

Ovarian Cancer

- Case-fatality rate is high
- Survival correlates with stage
- Symptoms develop late
- Screening for early disease in asymptomatic women may improve survival

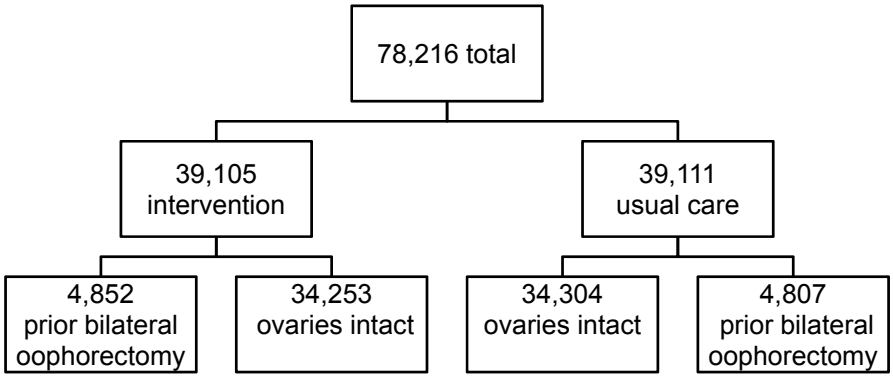
PLCO Cancer Screening Trial

- Randomized controlled trial of screening vs. usual care
- Primary objective: effect of screening on cancer-specific mortality
- Age 55 – 74 at entry
- 10 U.S. centers from 11/1993 – 7/2001

Ovarian Study Design

- Screening intervention
  - CA-125 annually for 6 years
  - TVU annually for 4 years
- 88% power to detect 35% reduction in mortality
- Compliance assumed >90% for CA-125; >85% for TVU
- Contamination assumed <10%

Females Randomized



Participant Characteristics

Characteristic	Intervention N=34,253	Usual Care N=34,304
Age (years)	%	%
55-59	34.2	34.2
60-64	30.4	30.3
65-69	21.8	21.9
70-74	13.6	13.6
Race		
White (non-Hispanic)	88.6	88.4
African-American (non-Hispanic)	5.7	5.7
Hispanic	1.5	1.5
Asian	3.4	3.6
Other	0.8	0.8

Participant Characteristics, cont.

Characteristic	Intervention N=34,253	Usual Care N=34,304
Education	%	%
Less than high school	6.6	6.5
High school graduate	40.0	40.5
Some college	23.1	22.7
College graduate	15.5	15.1
Postgraduate	14.8	15.2
Prior hysterectomy	27.3	27.2
Ever used oral contraceptives	53.6	54.1
Ever used hormone replacement therapy	63.4	63.0
Nulliparous	9.3	9.2
Personal history of breast cancer	3.6	3.6
Family history of breast or ovarian cancer	17.6	17.3

Follow-Up

	Intervention	Usual Care
Active or known dead	96.4%	96.1%
Median time	12.4 years	12.4 years

Compliance and Contamination

- Compliance with CA-125
  - 85% at baseline
  - 79% year 4
  - 73% year 6
- Compliance with TVU
  - 84% at baseline
  - 78% year 4
- Contamination
  - CA-125 2.3 – 3.2%
  - TVU 2.7 – 4.6%

Ovarian Cancers Diagnosed

- Incidence
  - 212 cases intervention
    - 5.7 cases/10,000 person - years
  - 176 cases usual care
    - 4.7 cases/10,000 person - years
  - Rate ratio 1.21 (95% CI 0.99-1.48)

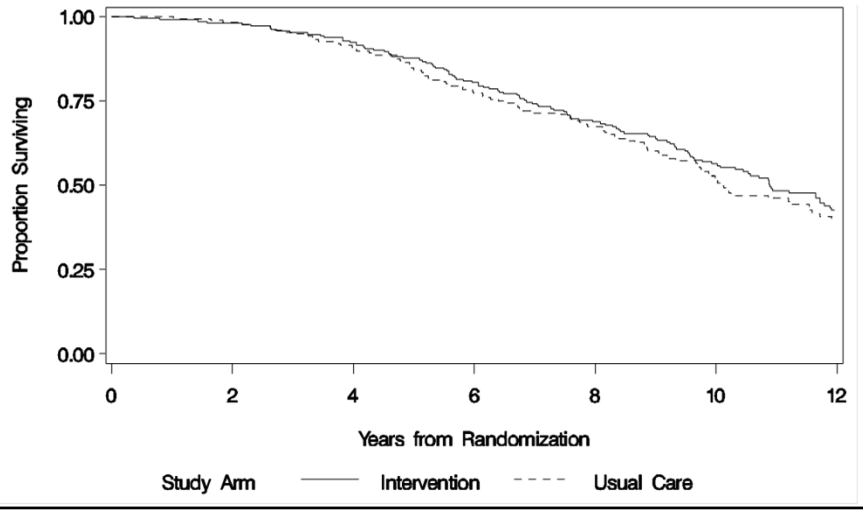
Stage

	Intervention			Usual Care		
Stage	**Study Years 0-5 N (%)**	**Study Years 6-12 N (%)**	**All N (%)**	**Study Years 0-5 N (%)**	**Study Years 6-12 N (%)**	**All N (%)**
I	19 (15)	13 (15)	32(15)	13 (13)	5 (6)	18 (10)
II	11 (9)	4 (5)	15 (7)	13 (13)	7 (9)	20 (11)
III	75 (60)	45 (52)	120 (57)	46 (46)	37 (48)	83 (47)
IV	20 (16)	23 (27)	43 (20)	27 (27)	27 (35)	54 (31)
Unk	1 (1)	1 (1)	2(1)	0	1 (1)	1 (1)
Total	126	86	212	99	77	176

Incidence and Mortality

- Incidence
  - 212 cases intervention
  - 176 cases usual care
  - Rate ratio 1.21 (95% CI 0.99-1.48)
- Mortality
  - 118 deaths intervention
    - 3.1 deaths/10,000 person - years
  - 100 deaths usual care
    - 2.6 deaths/10,000 person - years
  - Rate ratio 1.18 (95% CI 0.91-1.54)

Ovarian Cancer Survival From Date Of Randomization



Screening-Related Harms

- 3285 false positive
- 1080 surgery
- 163 patients had 222 major complications
  - Infection 89 (40%)
  - Direct surgical complication 63 (28%)
  - Cardiopulmonary 31 (14%)
  - Other 39 (18%)
- Oophorectomy rate
  - 7.7% intervention
  - 5.8% usual care
  - rate ratio 1.33 (CI 1.24 – 1.43)

Internet, 1998

PLEASE, PLEASE, **P-L-E-A-S-E** TELL ALL YOUR FEMALE FRIENDS AND RELATIVES TO **INSIST** ON A CA-125 BLOOD TEST EVERY YEAR AS PART OF THEIR ANNUAL PHYSICAL EXAMS. BE FOREWARNED THAT THEIR DOCTORS MIGHT TRY TO TALK THEM OUT OF IT, SAYING "IT ISN'T NECESSARY." BELIEVE ME, HAD I KNOWN THEN WHAT I KNOW NOW, WE WOULD HAVE CAUGHT MY CANCER MUCH EARLIER (BEFORE IT WAS A STAGE 3 CANCER)!!!

INSIST ON A CA-125 BLOOD TEST EVERY YEAR; DON'T TAKE "NO" FOR AN ANSWER.

IF YOUR DOCTOR WON'T RUN IT,

FIND A DIFFERENT DOCTOR.

Conclusions, 2011

- Screening with TVU annually for 4 years and CA-125 annually for 6 years did not reduce ovarian-cancer mortality
- There was evidence of harm from evaluation of false-positive screens
- Screening as performed in PLCO does not reduce disease-specific mortality