GYNECOLOGIC CANCER

Recent Advances in Management

Tate Thigpen, M.D.

Disclosure Information
James Tate Thigpen, M.D.

- **I have the following financial relationships to disclose:**
  - **Consultation: Clovis, Genentech, Merck, Oasmia, Tesaro**
  - **Speakers' Bureau Participation: Astra Zeneca, Clovis, Genentech, Novartis, Tesaro**

Gynecologic Cancer

Discussion Topics

- Ovarian Cancer
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506
- Cervical Cancer
  - Neoadjuvant Chemotherapy: ASCO 5523
- Uterine Cancer
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505

Gynecologic Cancer

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  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505

THE ROLE OF SURGERY IN FRONT-LINE MANAGEMENT

- ASCO Abstract 5500: JCOG 0602
- SGO Abstract 43: Retrospective Study of PDS and NACT

PDS v NACT: Phase III Studies

	EORTC PDS	EORTC NACT	CHORUS PDS	CHORUS NACT
Patients	336	334	276	274
Residual ≤1 cm	42%	81%	-	-
No Gross Residual	18%	45%	15%	35%
Median PFS	12	12	11	12
Median OS	29	30	23	24
HR for NACT in OS	0.98		0.87	
95% Confidence Interval	0.84-1.13		0.72-1.05	
Non-inferiority Margin	1.25		1.18	
P value	0.01		NA	

[1]Vergote et al: NEJM 2010
[2]Kehoe et al: ASCO 2013

JCOG
Japan Clinical Oncology Group

Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602.

Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Takehara K, Miyamoto K, Wakabayashi M, Okamoto A, Ushijima K, Kobayashi H, Kawana K, Yokota H, Takano M, Omatsu K, Watanabe Y, Yamamoto K, Yaegashi N, Kamura T, Yoshikawa H,

Japan Clinical Oncology Group

UMIN Clinical Trials Registry: UMIN000000523

Trial Design

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Multicenter (34 specialized institutions),
Randomized Phase III Trial

Clinically diagnosed Stage III/IV ovarian, tubal, and peritoneal cancers

Balancing factors
Institution, Stage III/IV
PS 0-1/2-3, Age <60/≥60

Randomization

Standard Arm (PDST)

PDS → 4x TC → 4x TC

PDS: primary debulking surgery

IDS* → 4x TC

*; Optional for pts with suboptimal PDS.
Mandatory for pts with any of Ut/Adn/OM Unremoved.

Experimental Arm (NACT)

NAC (4x TC) → IDS → 4x TC

IDS: interval debulking surgery

TC regimen: PTX 175 mg/m^2 iv, CBDCA AUC 6.0 iv

Patient Characteristics by Study

Characteristics	EORTC		CHORUS		JCOG	
	PDS N=336	NACT N=334	PDS N=276	NACT N=274	PDS N=149	NACT N=152
Median Age (yrs)	62	63	66	65	59	60.5
PS 2-3	12%	13%	20%	19%	13%	14%
Stage IV	23%	24%	25%	25%	33%	31%
CA-125 (median)	1130	1180	NA	NA	1950	1556.5
Clear/Mucinous	4%	4%	2%	8%	10%	5%

Initial Statistical Considerations

JCOG
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Planned sample size was 300
(Expected number of events was 276)

- One-sided alpha of 0.05
- Power of 0.8
- Expected 3-year OS
  PDST = 25%, NACT = 30.3%
- Non-inferiority margin = 5% in 3-year OS
  Corresponding HR of 1.161
- Accrual period: 3 years, Follow-up period: 5 years

Comparison of Treatment Invasiveness

JCOG Japan Clinical Oncology Group

Parameters for treatment invasiveness		PDST(n=149)	NACT(n=152)	P value
Average number of surgery		1.32	0.86	<0.0001
Median operation time (min)		341	273	<0.0001
Median Blood/Ascites loss (ml)		3447	619.5	<0.0001
Resection of	Abdominal organs	56(37.6%)	36(23.7%)	0.0121
	Distant metastases	16(10.7%)	6(3.9%)	0.0272
Transfusion*	RCC	97(66.0%)	79(52.7%)	0.0247
	FFP	42(28.6%)	25(16.7%)	0.0180
Post-operative G3/4 adverse events**		23(15.6%)	6(4.6%)	0.0029

*among all treated patients, **among all operated patients

Overall Survival (N=301)

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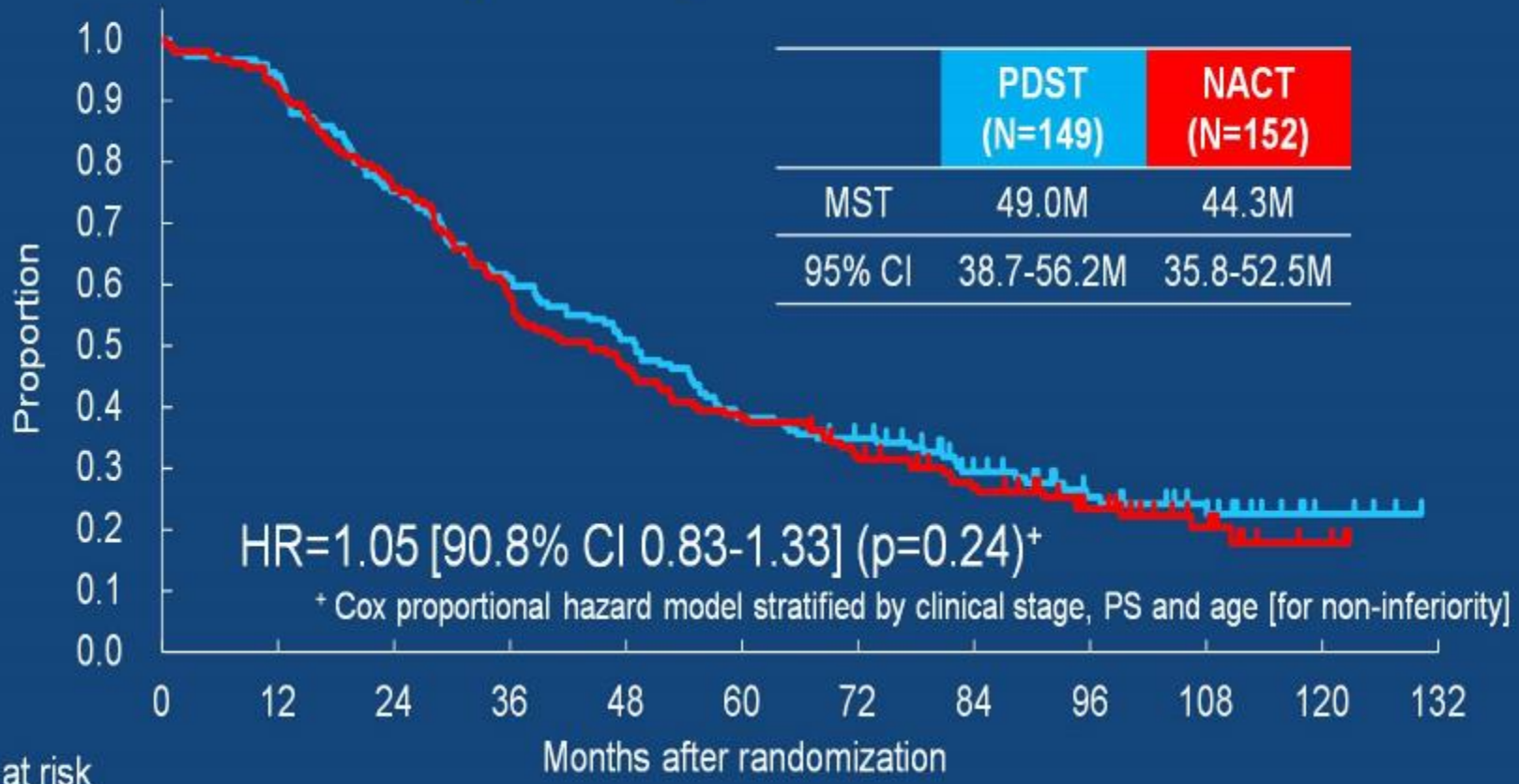
Japan Clinical Oncology Group



	PDST (N=149)	NACT (N=152)
MST	49.0M	44.3M
95% CI	38.7-56.2M	35.8-52.5M

Pts at risk

Arm A	149	140	112	91	76	57	50	34	22	15	4	0
Arm B	152	140	115	88	71	58	46	35	22	11	3	0

Progression-free Survival (N=301)

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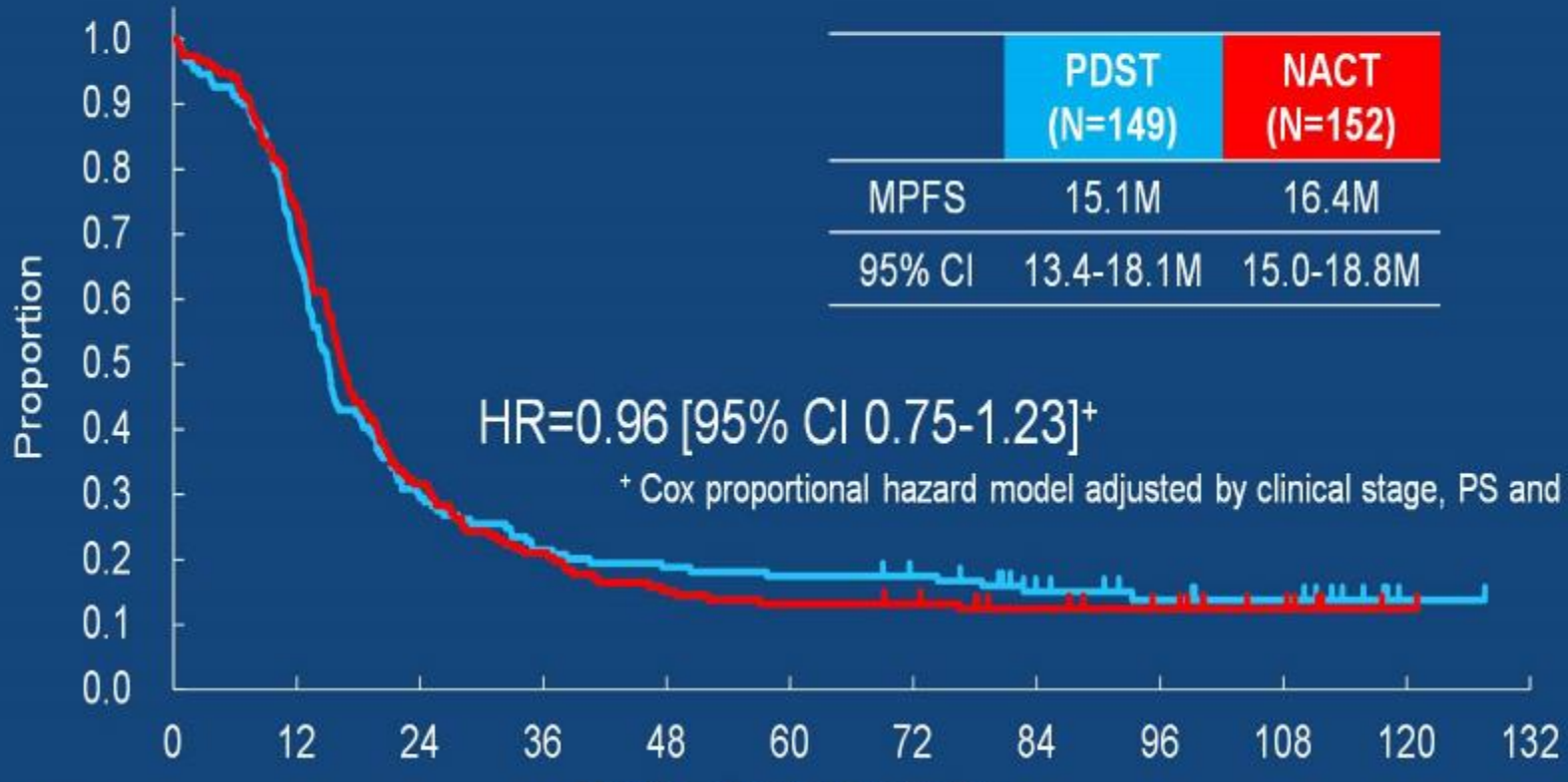
	PDST (N=149)	NACT (N=152)
MPFS	15.1M	16.4M
95% CI	13.4-18.1M	15.0-18.8M



Pts at risk

Arm A	149	99	44	32	28	26	24	15	11	9	1	0
Arm B	152	112	48	32	23	20	19	14	11	6	1	0

OS according to Debulking Results

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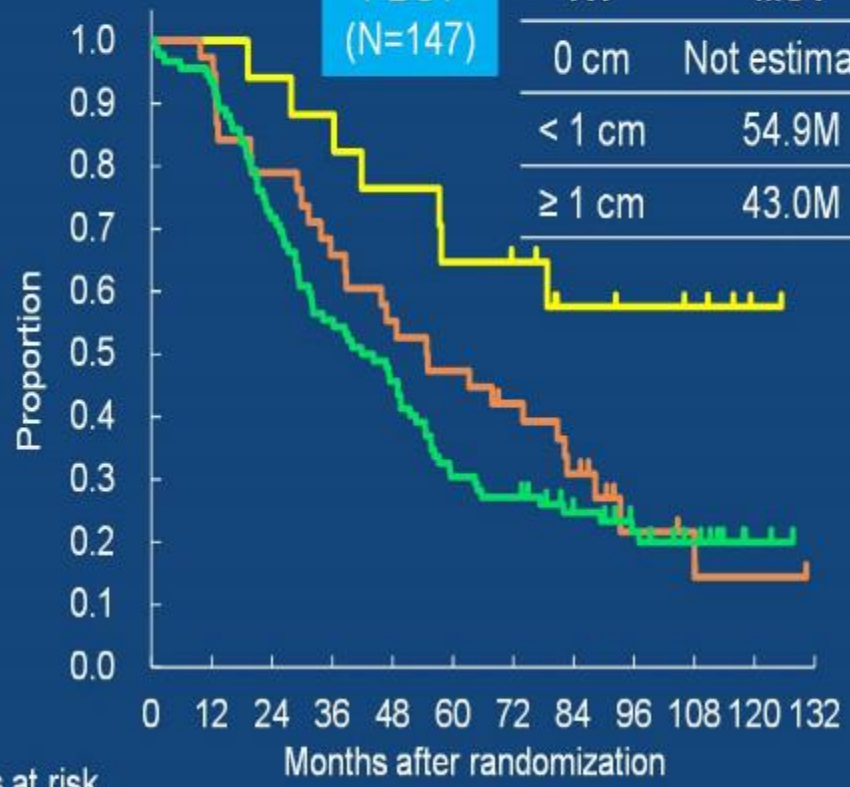
PDST (N=147)

RT	MST
0 cm	Not estimable
< 1 cm	54.9M
≥ 1 cm	43.0M

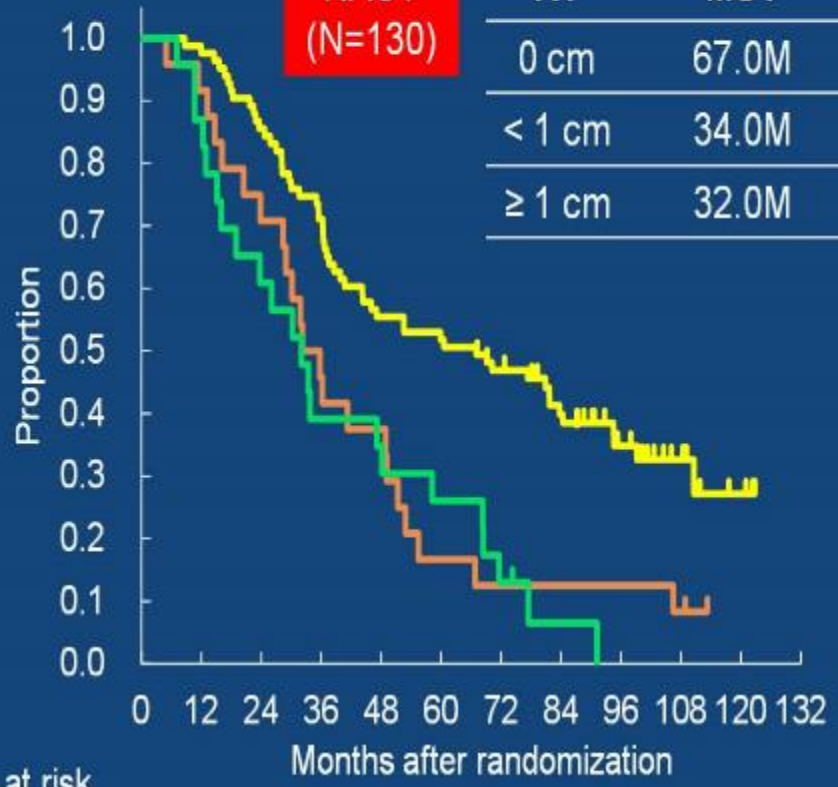


Pts at risk

RT = 0cm	17	17	16	15	13	11	10	6	5	4	1	0
RT < 1cm	38	37	30	25	21	18	15	10	4	3	1	0
RT ≥ 1cm	92	86	66	51	42	28	25	18	13	8	2	0

NACT (N=130)

RT	MST
0 cm	67.0M
< 1 cm	34.0M
≥ 1 cm	32.0M



Pts at risk

RT = 0cm	83	81	71	59	46	43	37	28	17	8	3	0
RT < 1cm	24	22	17	11	9	4	3	3	3	2	0	0
RT ≥ 1cm	23	20	14	9	8	6	3	1	0	0	0	0

PDS v NACT: Bottom Line

- **Overall results suggest that PDS and NACT yield equivalent results; either is acceptable**
- **Achieving optimal cytoreduction after NACT is not the same as achieving this with PDS (Manning-Geist et al, SGO 2018 abstract 43)**
- **Caveats**
  - **Patients with poor performance status or other indicators of poor general health may be better served with NACT**
  - **Variability in optimal debulking rate raises concerns about the quality of surgery across the studies**
  - **Results in the JCOG study support the need for an experienced, aggressive surgeon for best results**

Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

Patients with ≤1 cm Disease by Country

	Total	PDS (n = 329)	NACT -> IDS (n = 339)*
Belgium (n=133)	83%	72%	94%
Argentina (n=48)	71%	68%	74%
The Netherlands (n=104)	59%	40%	77%
Sweden (n=23)	59%	40%	75%
Norway (n=82)	55%	35%	73%
Italy (n=38)	52%	40%	64%
Spain (n=62)	49%	44%	58%
UK (n=101)	47%	37%	63%
Canada (n=84)	44%	29%	59%

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- **Caveats**
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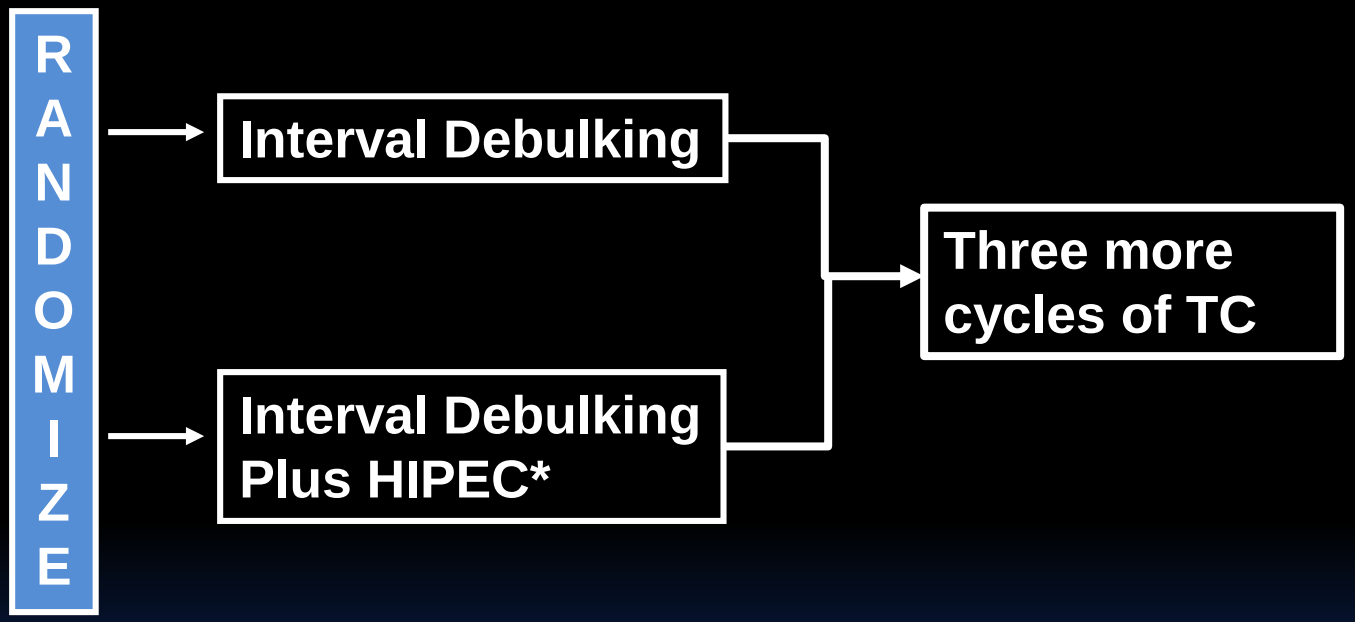
HIPEC

- NEJM 378:230-240, 2018

Ovarian Carcinoma

Hyperthermic Intraperitoneal Chemotherapy

- Stages III-IV
- At least stable disease after 3 cycles of TC
- Primary Endpoint: RFS
- N = 245



*HIPEC by open technique
- 40°C (104°F)
- Cisplatin 100 mg/m^2
- 120 minutes

Van Driel et al: NEJM 378:230-240, 2018

Ovarian Carcinoma

Hyperthermic IP Chemotherapy

Results

	Patients	RFS	OS	AEs (% G 3-4)
IDS	123	10.7 mos	33.9 mos	25%
IDS+HIPEC	122	14.2 mos	45.7 mos	27%
HR (CI)		0.66 (0.50-0.87)	0.67 (0.48-0.94)	
P		0.003	0.02	

* **Primary endpoint RFS (Relapse-Free Survival)**

Van Driel et al: NEJM 378:230-240, 2018

IDS +/- HIPEC: Bottom Line

- Randomized patients were stratified according to whether the surgical was R0 or one or more gross nodules ≤10mm diameter
- Significant improvement in RFS and OS
- Patients with grade 3-4 adverse effects: no difference between treatment arms
- Caveats
  - Overall surgical quality not clear
  - Relatively small trial
  - No bevacizumab
  - No excess toxicity
  - No confirmatory trial as of yet – need to await confirmation

SECONDARY SURGICAL CYTOREDUCTION

- **ASCO Abstract 5501: GOG 213**

A Phase III Randomized Controlled Trial of Secondary Surgical Cytoreduction followed by Platinum-Based Combination Chemotherapy, With or Without Bevacizumab in Platinum-Sensitive, Recurrent Ovarian Cancer: A NRG Oncology/Gynecologic Oncology Group Study

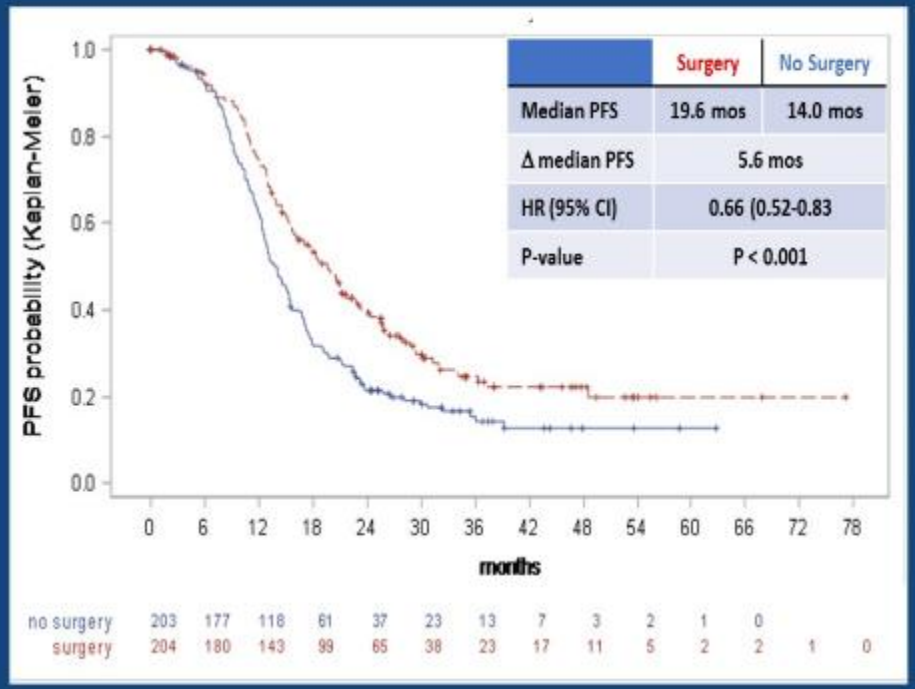
Robert L. Coleman, Nick Spirtos, Danielle Enserro, Thomas J. Herzog, Paul Sabbatini, Deborah Kay Armstrong, Byoung Kim, Keiichi Fujiwara, Joan L. Walker, Patrick J. Flynn, Angeles Alvarez Secord, David E. Cohn, Mark F. Brady, Robert S. Mannel

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: ROBERT L. COLEMAN, MD

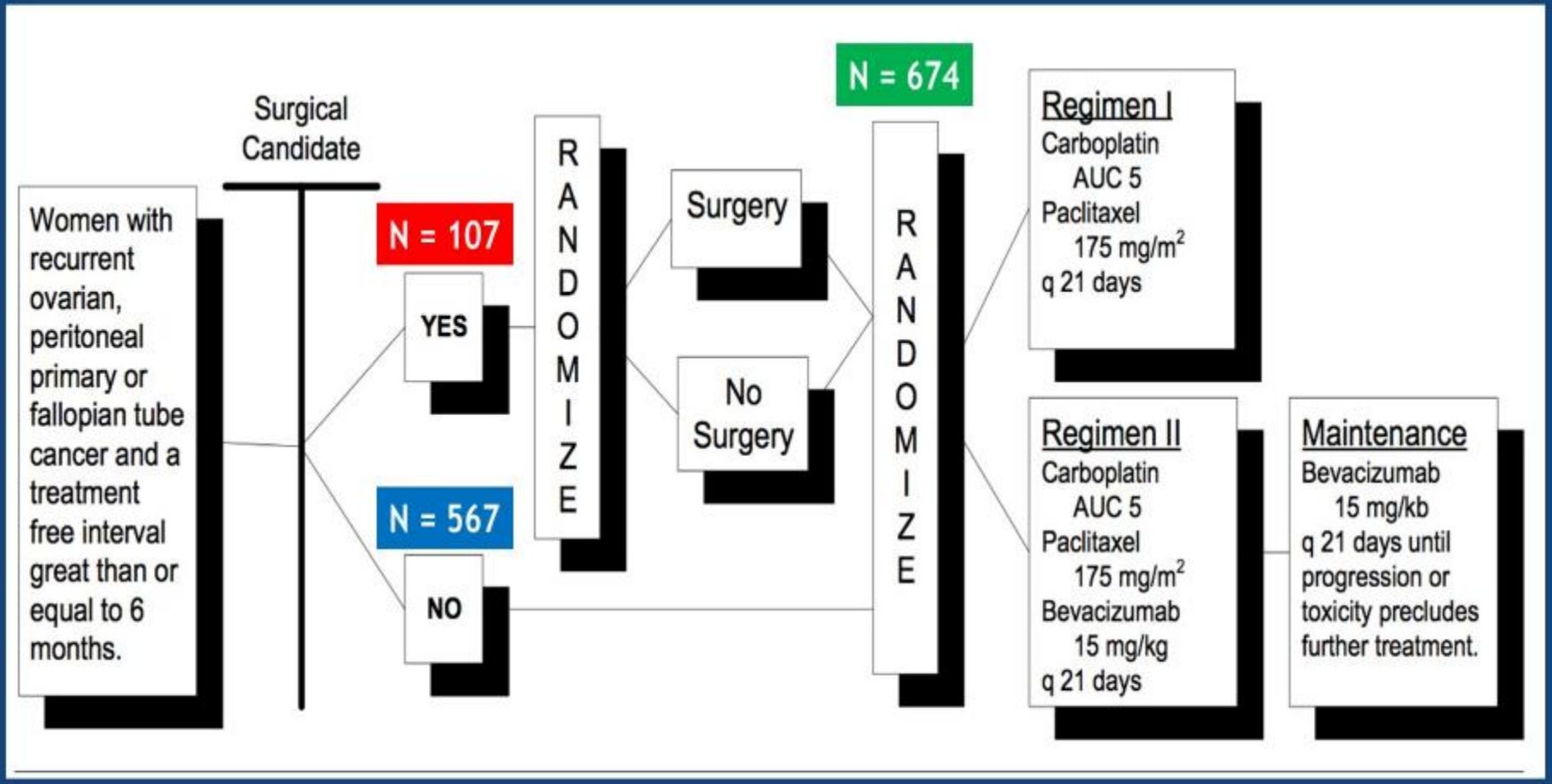
Background: DESKTOP III

- Surgery was safe and feasible
- R0 rate: 72.5%
- Patients with residual disease after surgery had the same HR_{PFS} as those receiving chemotherapy alone
- Time to 3rd line significantly longer
- OS: immature at interim analysis

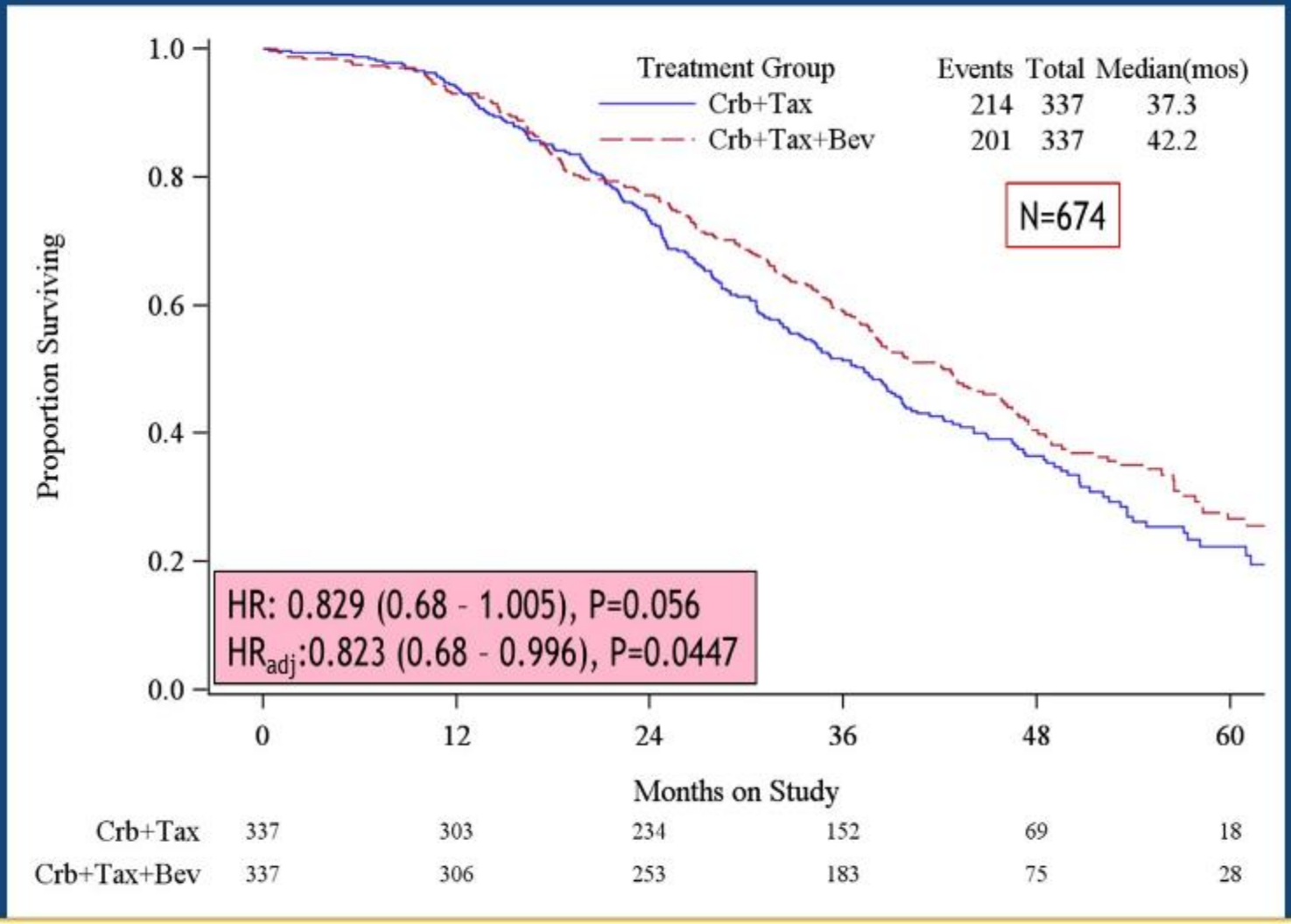


DuBois, Proc ASCO, Abst 5501, 2017

GOG 213: Schema Objective #1

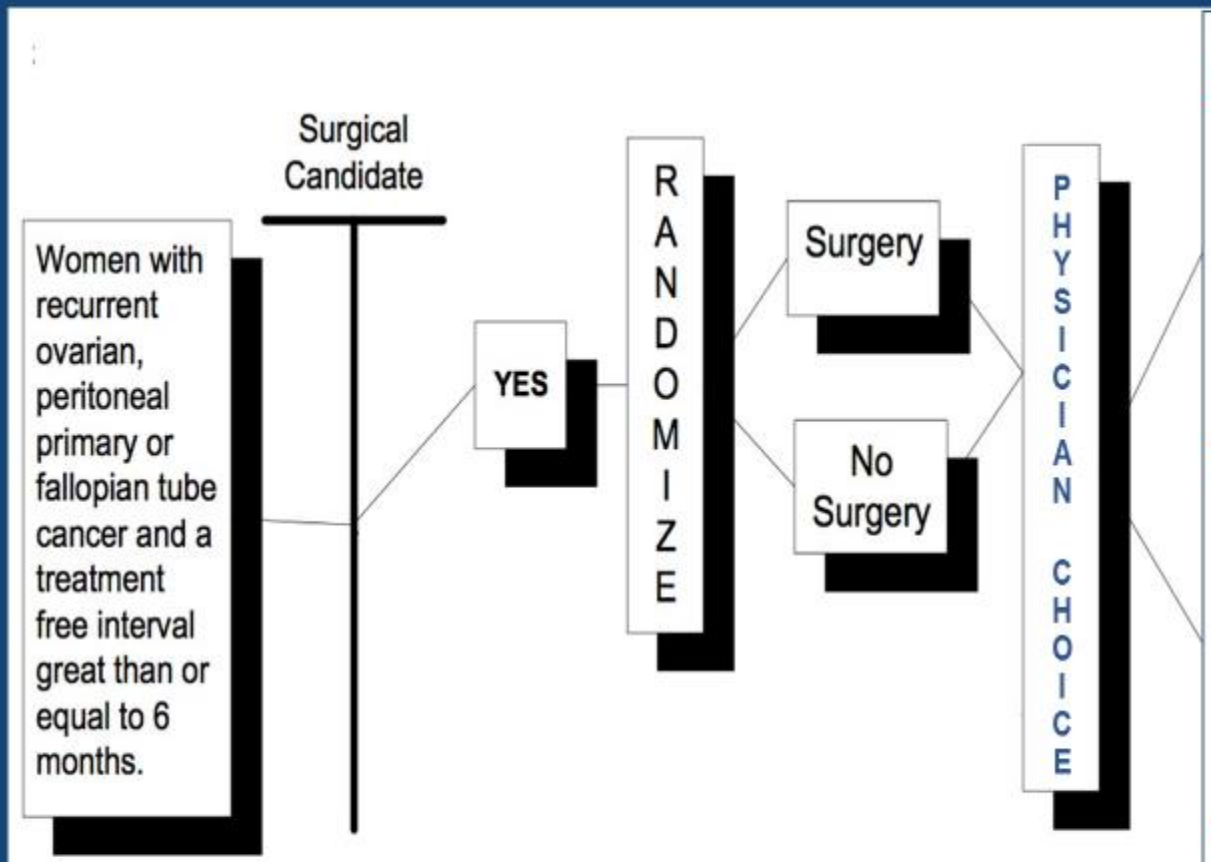


GOG 213 Objective 1: OS



Coleman RL, Lancet Oncol 2017

GOG 213: Schema Modification 8/29/2011



Chemotherapy (2 options):

- Paclitaxel 175 mg/m^2 +
- Carboplatin AUC5

- Gemcitabine 1000 mg/m^2 d1,8 +
- Carboplatin AUC5

Bevacizumab (optional):

- 15 mg/kg
- Starting cycle 2 for post-op to a max of 8 cycles
- Maintenance allowed until progression, intolerance or death

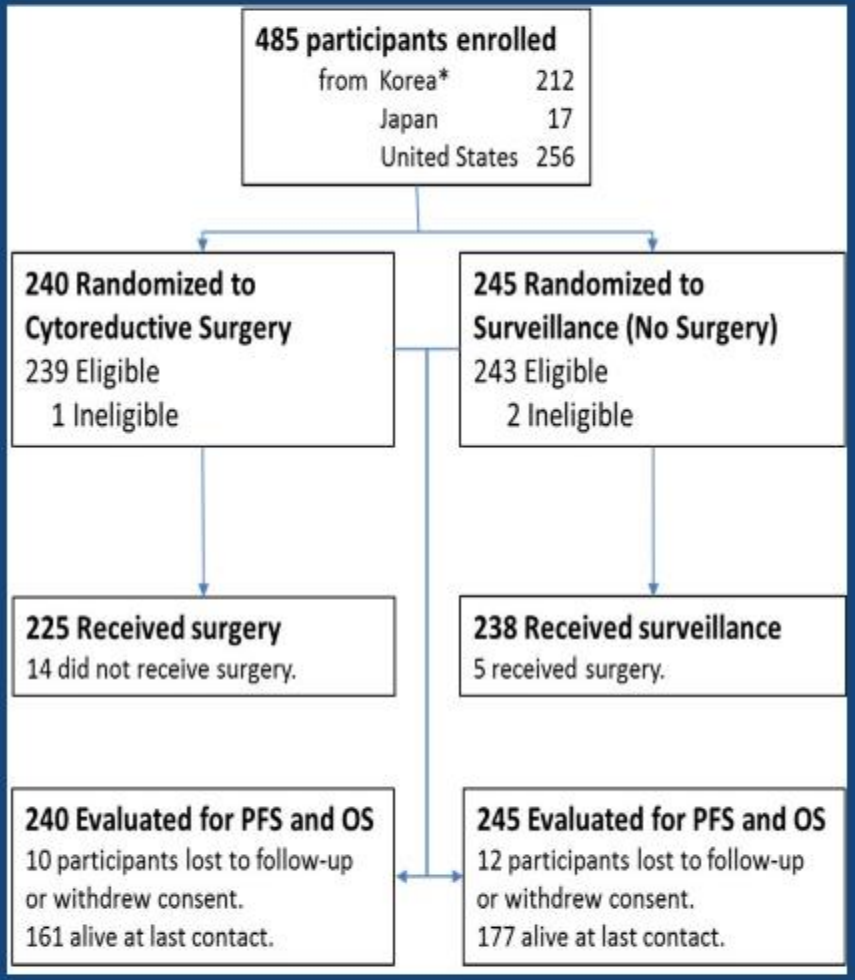
Cycle Length: 21 days

Statistical Design

- Primary endpoint: OS
- Assumption of no interaction between the two randomizations (Objective 1 patients, N=107)
- Alpha set two-sided at 0.05 in each randomized comparison
- Stratification variables:
  - Platinum-Free Interval (6-12, ≥12 months)
  - Chemotherapy regimen chosen (4 options)
- Targeted adjusted HR: 0.70 (increase from 50% to 61.5% at 22 months)
- Analysis considered mature: 250 events

CONSORT and Accrual

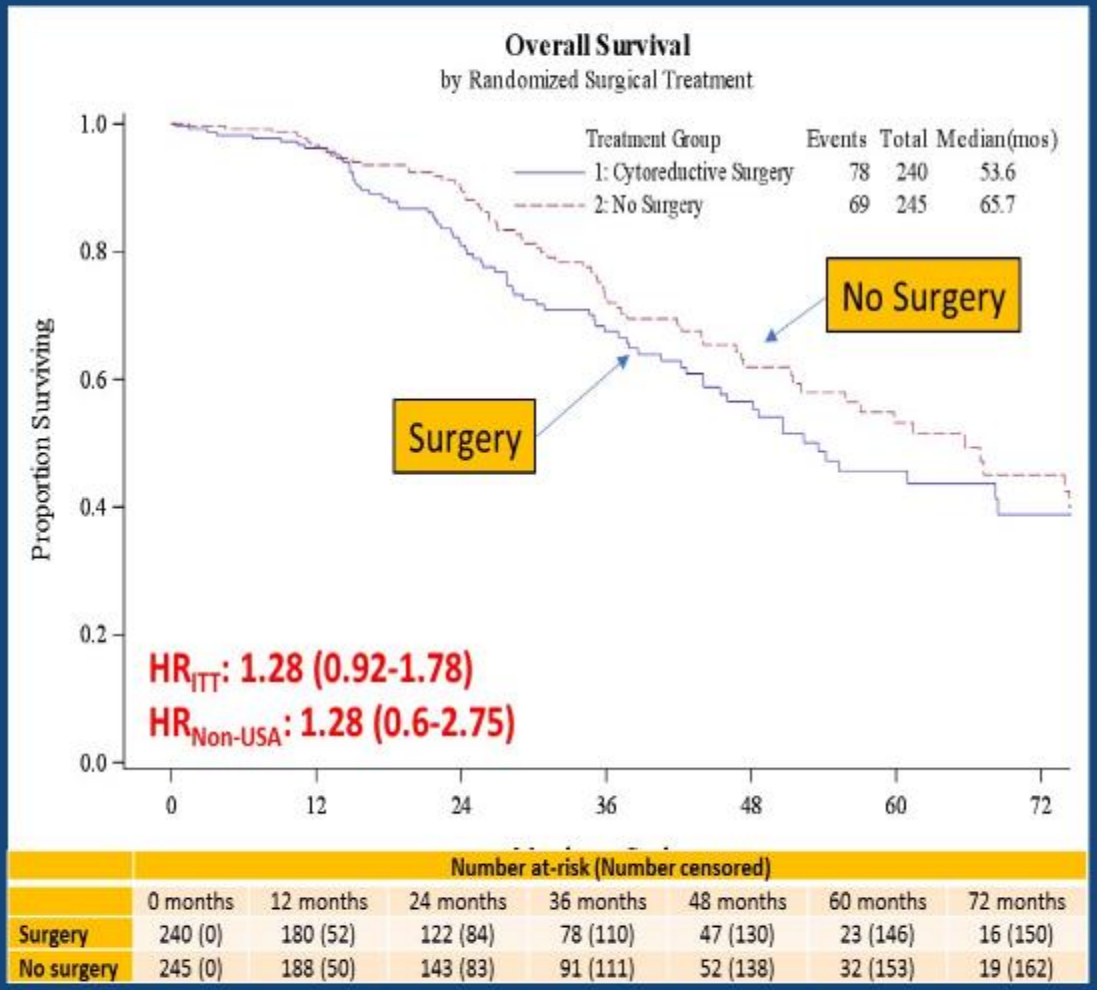
Opened: Dec 6, 2007
Closed: Jun 9, 2017



Surgical Findings

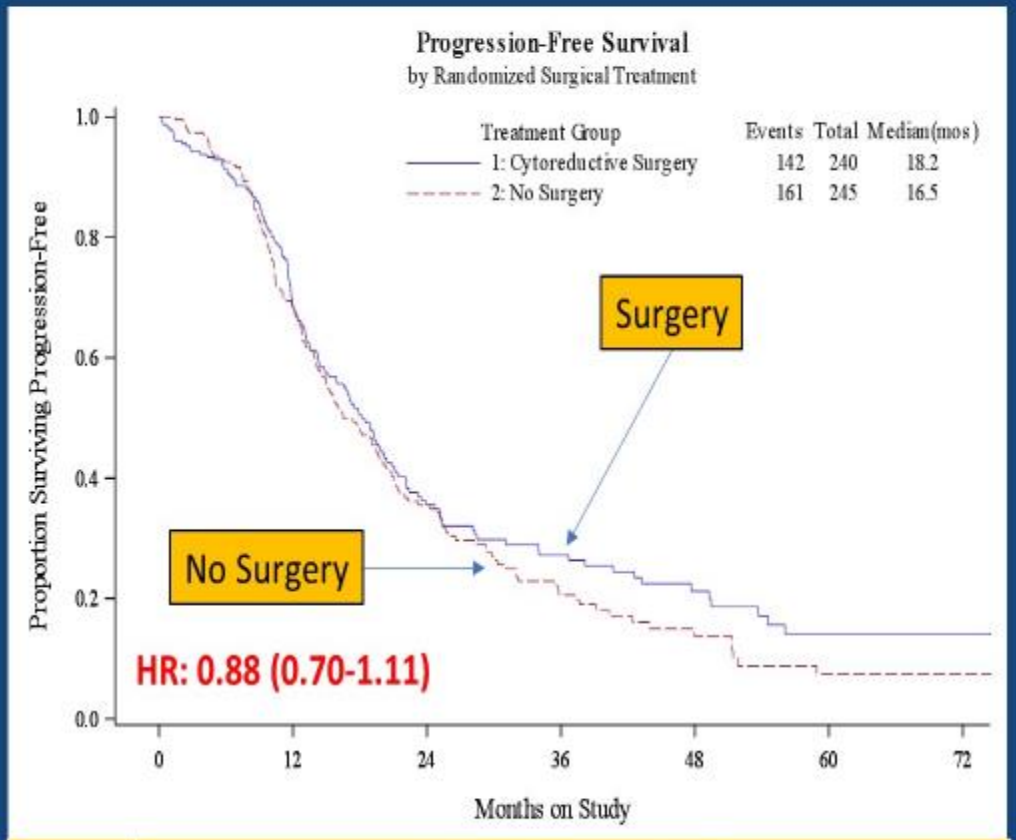
- Surgical outcomes: (ITT population)
  - R0 = 64% (146/230)
  - 14 patients did not undergo surgery
- Surgical outcomes (Per protocol population)
  - **R0 = 68% (146/216)**
- Median duration of follow-up: 34.6 months

Primary Endpoint OS: Surgery vs. No Surgery



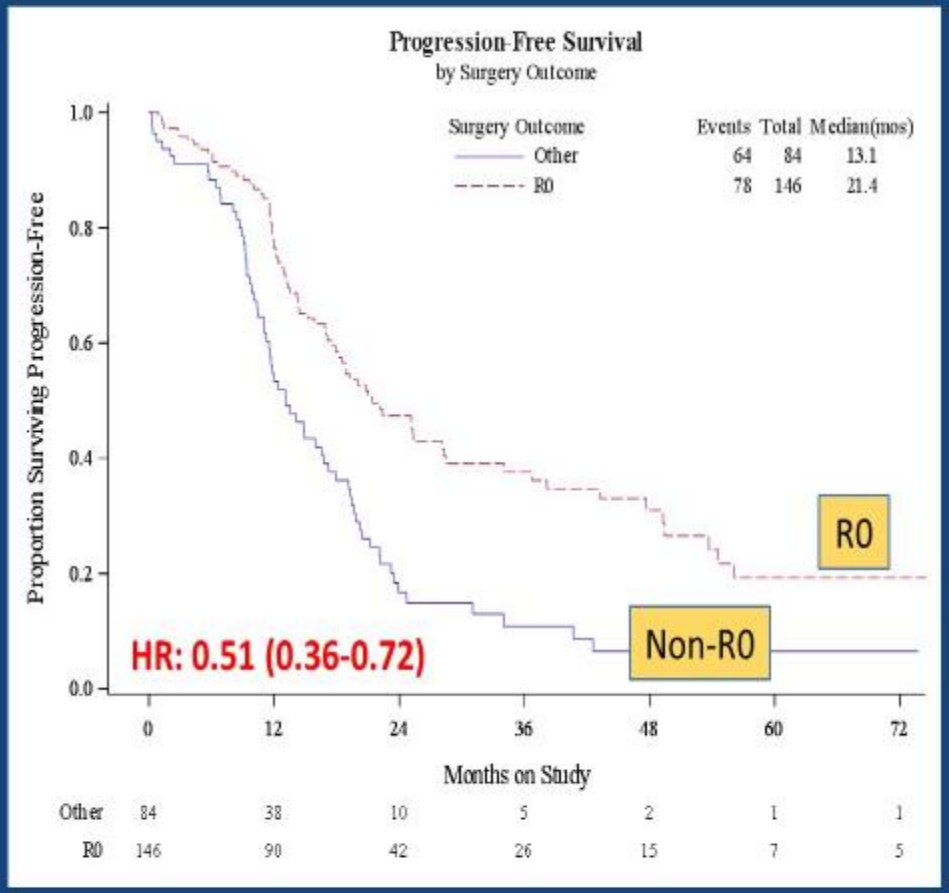
	Number at-risk (Number censored)						
	0 months	12 months	24 months	36 months	48 months	60 months	72 months
Surgery	240 (0)	180 (52)	122 (84)	78 (110)	47 (130)	23 (146)	16 (150)
No surgery	245 (0)	188 (50)	143 (83)	91 (111)	52 (138)	32 (153)	19 (162)

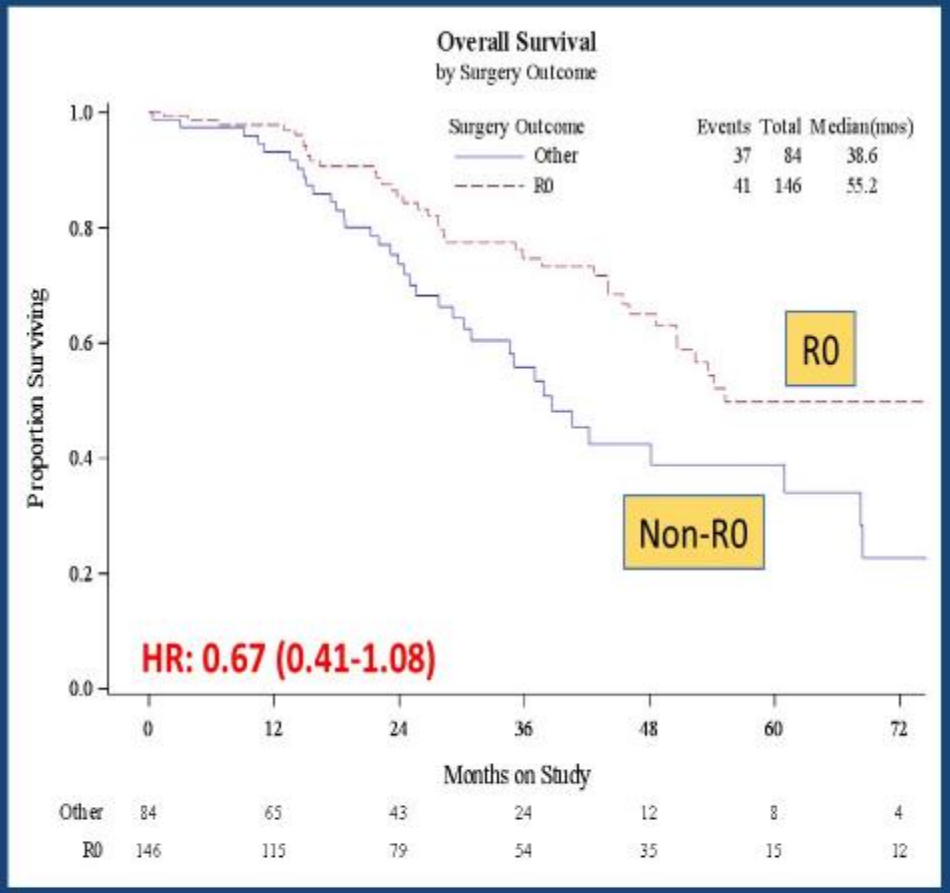
Secondary Endpoint PFS: Surgery vs. Chemo



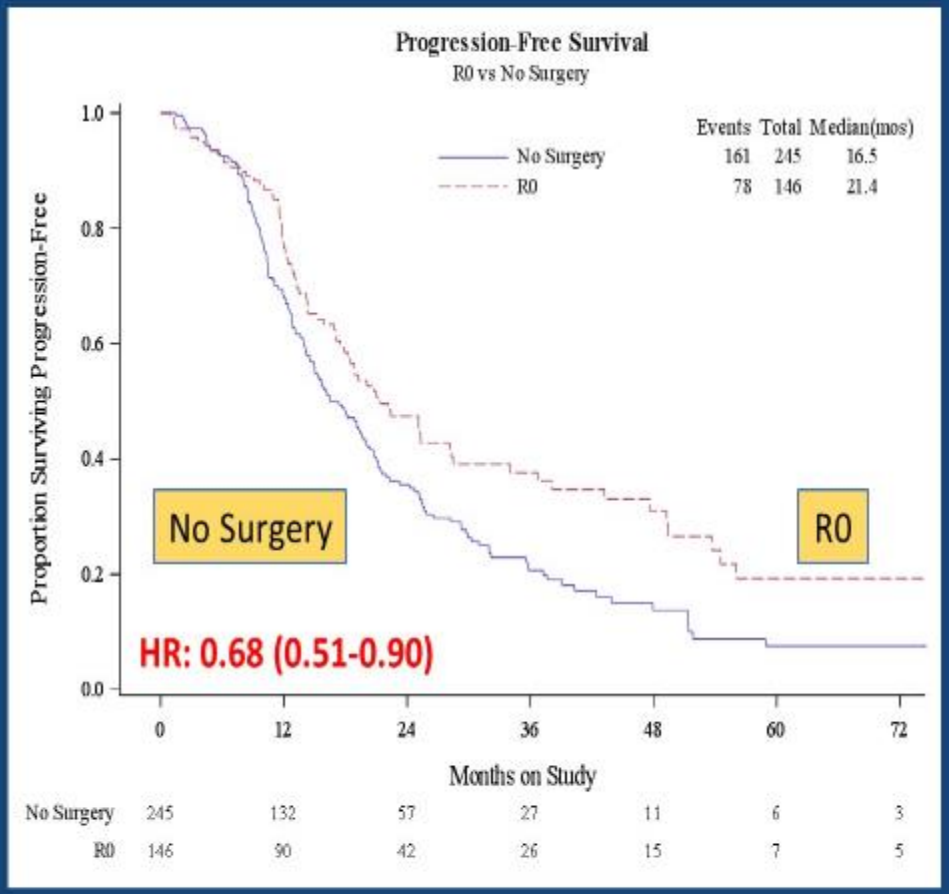
	Number at-risk (Number censored)						
	0 months	12 months	24 months	36 months	48 months	60 months	72 months
Surgery	240 (0)	128 (48)	52 (68)	31 (78)	17 (86)	8 (90)	6 (92)
No surgery	245 (0)	132 (45)	57 (61)	27 (69)	11 (78)	6 (78)	3 (81)

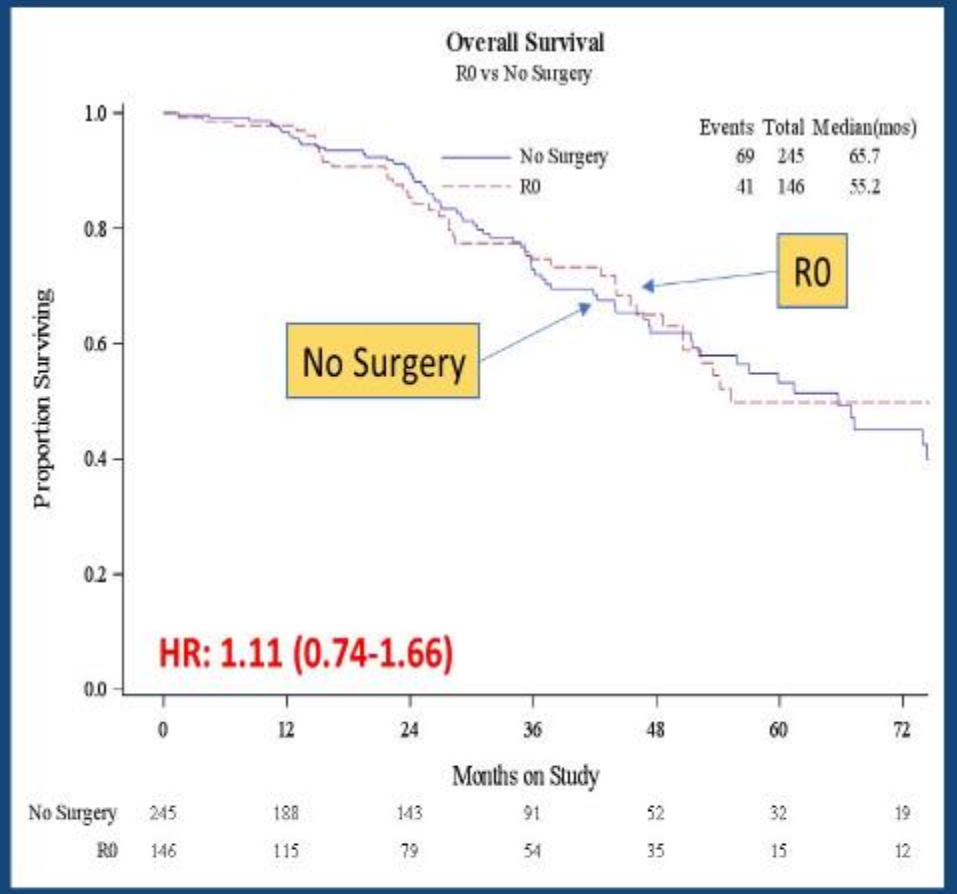
Exploratory Endpoint: Surgery Outcome R0 vs. Non-R0





Exploratory Endpoint: Surgical R0 vs. No Surgery





GOG 213: Adverse Events of Special Interest

Patients, %	No Surgery (n=233)	Surgery (n=224)	P
Allergy, grades ≥ 3	12 (5%)	12 (5%)	NS
Constitutional Symptoms, grades ≥ 3	8 (3%)	8 (2%)	NS
Cardiac, grades ≥3	20 (9%) – 1 death	24 (11%)	NS
Dermatological, grades ≥ 3	2 (1%)	5 (2%)	NS
Gastrointestinal, grade ≥ 3	15 (7%)	25 (11%)	NS
Perforation, necrosis, fistula, grade ≥ 3	2 (1%)	3 (1%)	NS
Hemorrhage/Bleeding, grade ≥3	1 (<1%)	3 (1%)	NS
Hematological, grade ≥ 3	191 (82%)	180 (80%)	NS
Infection, grade ≥3	30 (13%)	28 (13%)	NS
Metabolic, grade ≥3	32 (14%)	41 (18%)	NS
Neuropathy, grades ≥ 2	50 (21%)	44 (20%)	NS
Vascular grades ≥ 3	4 (2%)	7 (3%) – 2 deaths	NS

Secondary Surgical Cytoreduction: Bottom Line

- **Secondary surgical cytoreduction that achieves R0 disease status yields an improved PFS compared to those who undergo no surgery.**
- **Caveats**
  - **In surgical candidates, R0 status can be achieved 68-72% of the time with minimal added toxicity.**
  - **Comparison of R0 patient to those with no surgery (chemotherapy only) shows improved PFS, no difference in OS.**
    - **This is consistent with trials assessing other approaches: improved PFS but no OS difference.**
    - **The lack of OS difference probably results from the extensive post-progression therapy these patients receive which renders OS an uninterpretable endpoint.**

Gynecologic Cancer

Discussion Topics

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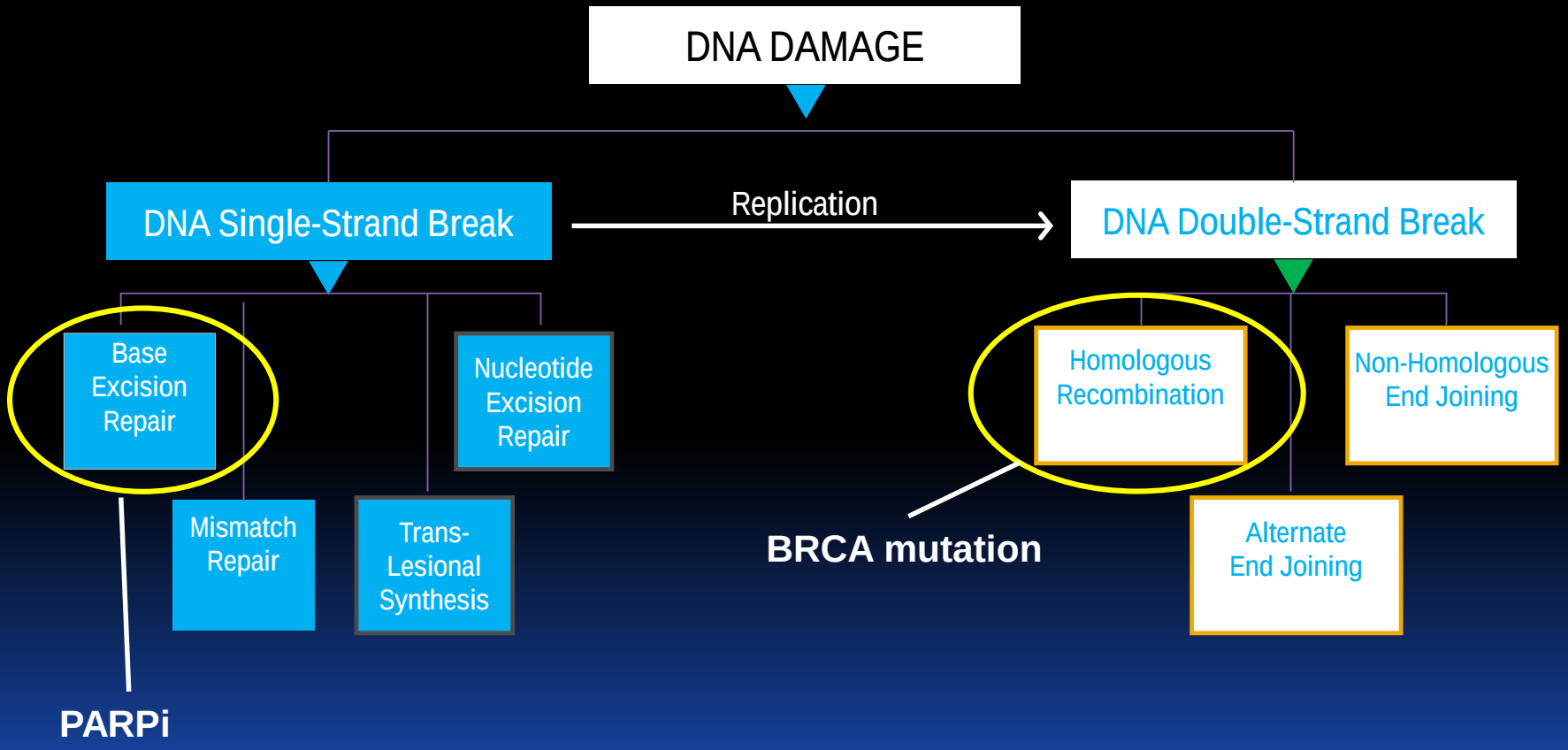
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506
- Cervical Cancer
  - Neoadjuvant Chemotherapy: ASCO 5523
- Uterine Cancer
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505

PARP INHIBITORS AND MAINTENANCE THERAPY FOR OVARIAN CANCER

- ASCO Abstract 5508: Cost Effectiveness of Maintenance
- ASCO Discussions: Aghajanian and Tian
- SGO Abstracts
  - 16: PARPi Cost Effectiveness
  - 19: Clinical Benefit of Maintenance Rx
  - 21: Niraparib Cost Effectiveness
- PARPi maintenance registration trials

PARP Inhibitors

DNA REPAIR



Ovarian Carcinoma

GERMLINE AND SOMATIC *BRCA* MUTATIONS[1-4]

	Germline	Somatic
Prevalence	18%	7%
Origin	Inherited	Acquired
Location	All cells in the body	Only in tumor cells

1. Pennington et al. Clin Cancer Res. 2014;20(3):764-75
2. Hennessy et al. J Clin Oncol. 2010;28(22):3570-6. **3.** Petrucelli et al. In:
3. Pagon et al, eds. *GeneReviews® [Internet*]. https://www.ncbi.nlm.nih.gov/books/NBK1247/. Updated September 26, 2013.
4. Robson et al. J Clin Oncol. 2015;33(31):3660-7.

Ovarian Carcinoma: HRD+

- In addition to BRCA1 and BRCA2, other genetic aberrations can induce homologous recombination repair deficiency including:
  - Genes in the Fanconi anemia pathway such as RAD51C, RAD51D, BRIP1, PALB2, BARD1
  - Mismatch repair genes such as MLH1, MSH2
- These other genes accounting for HRD+ involve up to 25% of ovarian cancer patients
- In total, as much as 50% of ovarian cancer patients exhibit deficiency of homologous recombination repair
- While PARPi have their greatest impact in patients with BRCA mutations and other genes producing HRD, even wild-type patients benefit from PARPi.

Companion Diagnostics - BRCA

Companion Diagnostic	Company	Sample	Genes Assessed	Type(s) of Analysis	Results	Drug
BRACAnalysis CDx	Myriad Genetics	Whole blood	g*BRCA1* g*BRCA2*	Sanger sequencing and multiplex PCR	*BRCA1/2* status Germline	Olaparib Complementary Diagnostic: Maintenance
FoundationFocus CDx BRCA	Foundation Medicine	FFPE	Tumor *BRCA*	Next generation sequencing	*BRCA 1/2* status Germline + Somatic	Rucaparib

FFPE: Formalin fixed paraffin embedded
https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm

Companion Diagnostics - HRD

Companion Diagnostic	Company	Sample	Genes Assessed	Type(s) of Analysis	Results	Studies
myChoice HRD (Includes Tumor BRACAnalysis CDx)	Myriad Genetics	FFPE	Tumor BRCA1/2; Tumor Genomic Instability	LOH, LST, TAI	**HRD Score:** HRD high (≥42 or *BRCAmut*) HRD low (<42 & *BRCAwt*)	Niraparib Olaparib Veliparib
FoundationFocus CDxBRCA LOH	Foundation Medicine	FFPE	324 genes	Base substitutions, insertion/deletions (indels), CNAs, select gene rearrangements, microsatellite instability (MSI) and tumor mutational burden (TMB)	HRD LOH Cutoff: High LOH (≥16% genomic LOH) Low LOH (<16% genomic LOH)	Complementary Diagnostic: Rucaparib

FFPE: Formalin fixed paraffin embedded; LOH: Loss of heterozygosity; LST: Large scale state transitions; TAI: Telomeric allelic imbalance; CNA: Copy number alteration

PARP Inhibitors

- Maintenance

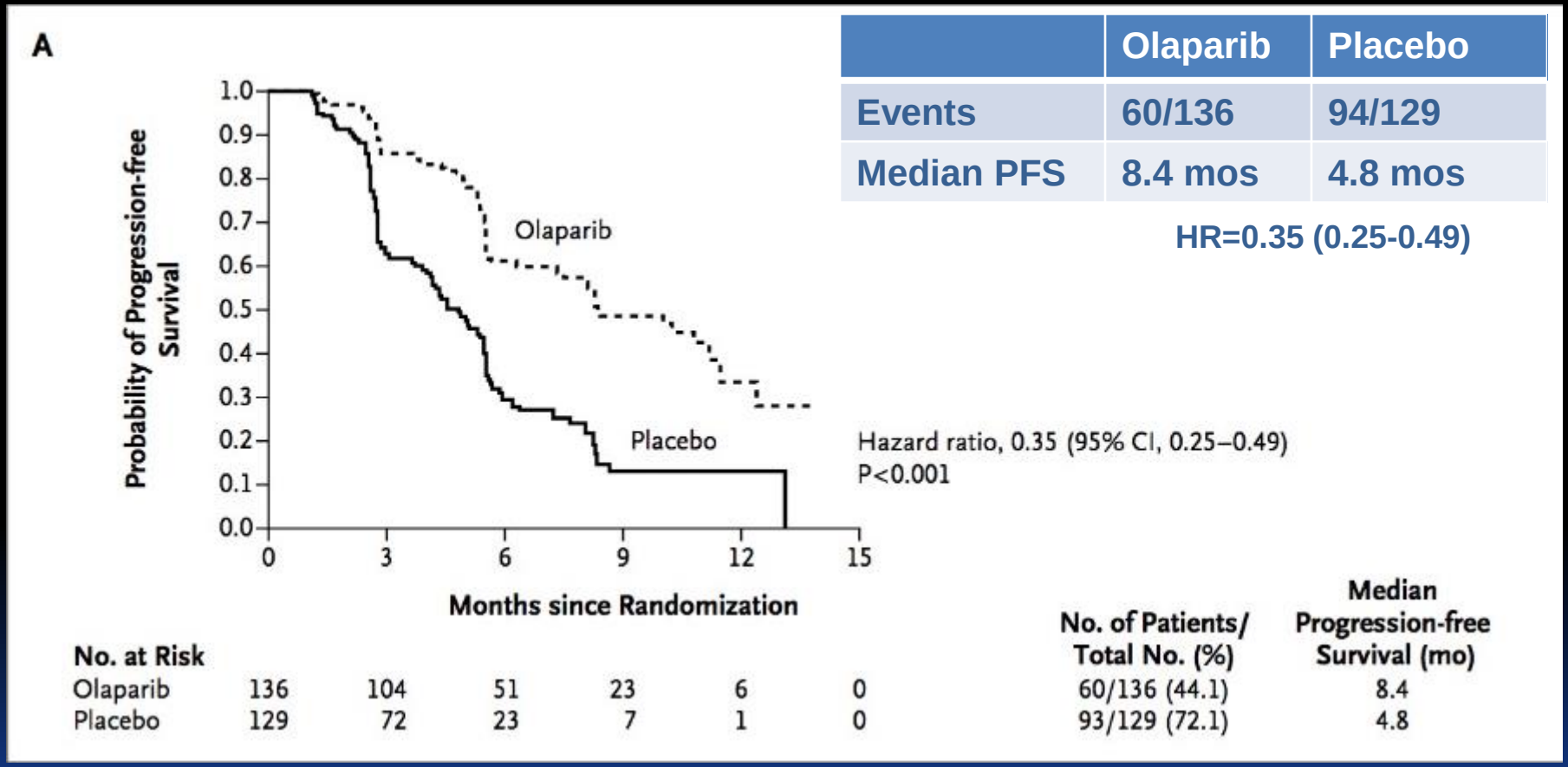
2nd or Greater Remission (CR or PR)	
Niraparib	NOVA
Olaparib	Study 19 SOLO2
Rucaparib	ARIEL3
First Remission	
Niraparib	PRIMA
Olaparib	SOLO1 (g*BRCA*)
Veliparib	GOG3005

- Treatment

PARPi	Study	N	ORR	DOR (months)
Niraparib	QUADRA g/s*BRCA*	55	31% ≥3 priors	9.4
Olaparib	Study 42 g*BRCA*	193	34% ≥3 priors	7.9
Rucaparib	Study 10 ARIEL2 g/s*BRCA*	106	54% ≥2 priors	9.2
Veliparib	GOG280 g*BRCA*	50	26% 1-3 priors	8.2

N Engl J Med. 2016 Dec 1;375(22):2154-2164, N Engl J Med. 2012 Apr 12;366(15):1382-92, Lancet Oncol. 2017 Sep;18(9):1274-1284, Lancet 2017 Oct 28;390(10106):1949-1961, Gynecol Oncol. 2016 Feb;140(2):199-203, Gynecol Oncol. 2017 Nov;147(2):267-275, Gynecol Oncol. 2015 Jun;137(3):386-91

Study 19: PFS in PSOC (Olaparib)



	Olaparib	Placebo
Events	60/136	94/129
Median PFS	8.4 mos	4.8 mos

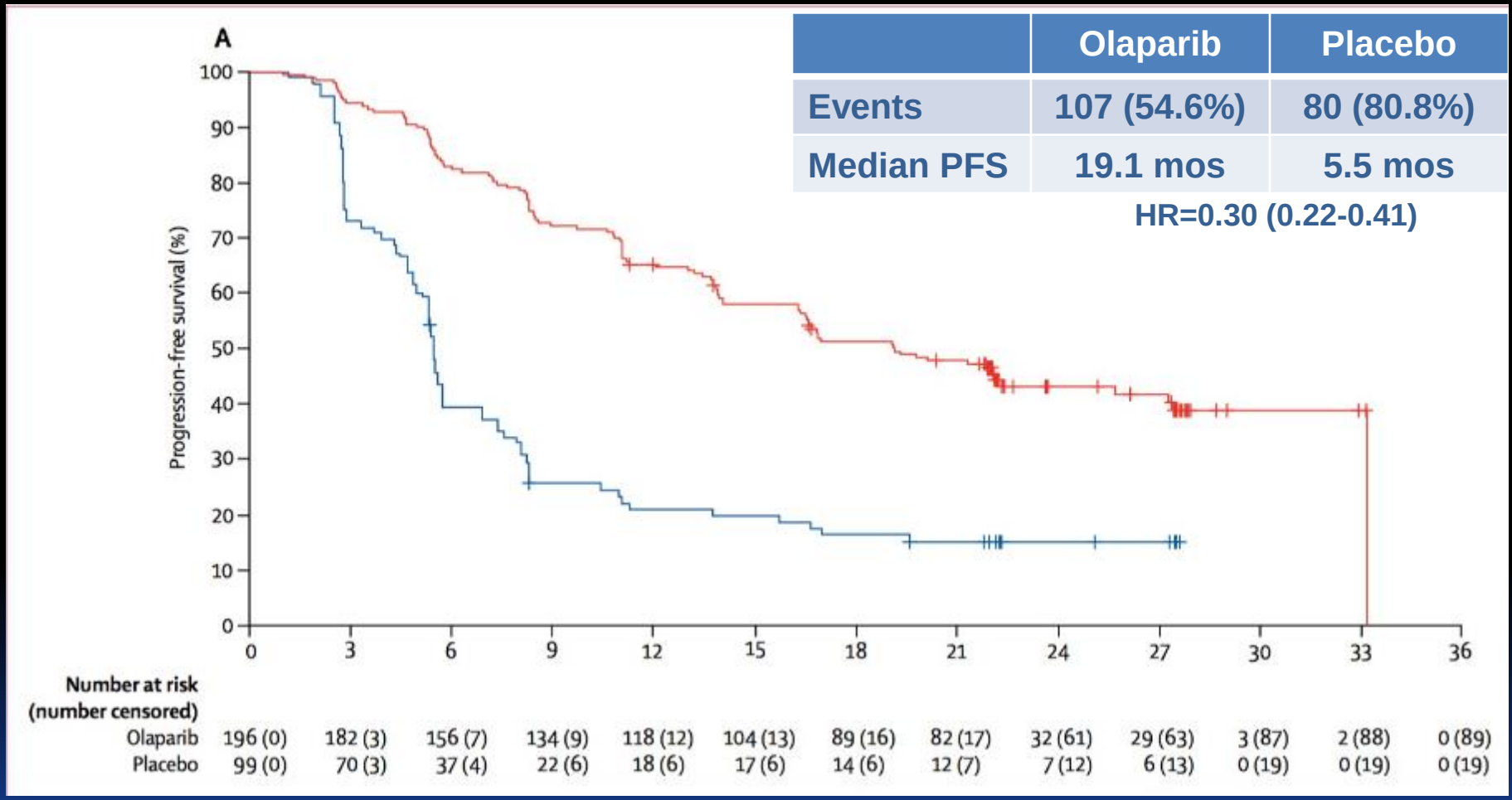
HR=0.35 (0.25-0.49)

Ledermann et al: NEJM 366:1382-1392, 2012

SOLO-2: PFS in BRCA+ Pts (Olaparib)

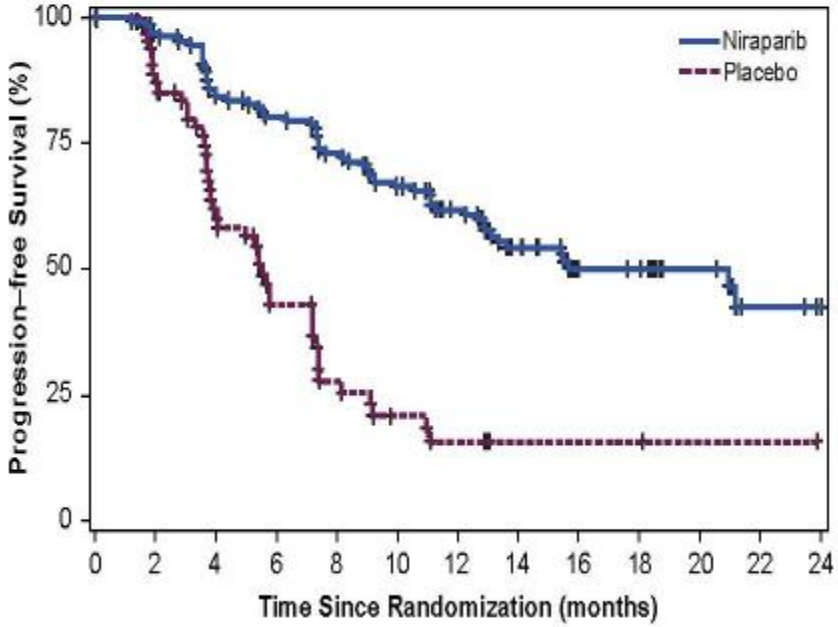
	Olaparib	Placebo
Events	107 (54.6%)	80 (80.8%)
Median PFS	19.1 mos	5.5 mos

HR=0.30 (0.22-0.41)



Pujade-Lauraine et al: Lancet Oncol 18:1274-1284, 2017

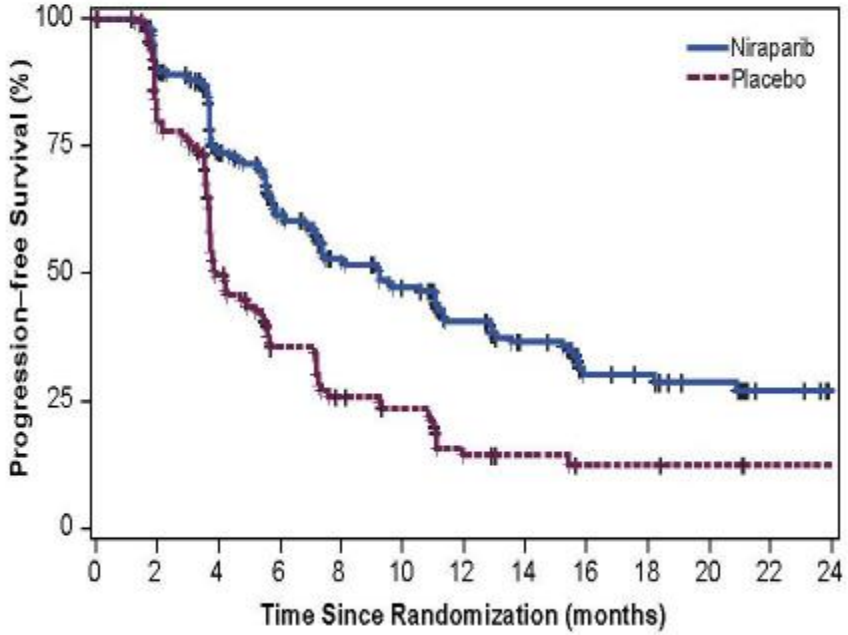
NOVA g*BRCA*mut Progression Free Survival



Treatment	PFS Median, months (95% CI)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (n=138)	21.0 (12.9, NR)	0.27 (0.173, 0.410) p<0.0001	62%	50%
Placebo (n=65)	5.5 (3.8, 7.2)		16%	16%

N Engl J Med. 2016 Dec 1;375(22):2154-2164

NOVA Non-g*BRCA*mut Progression Free Survival



Treatment	PFS Median, months (95% CI)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (n=234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) p<0.0001	41%	30%
Placebo (n=116)	3.9 (3.7, 5.5)		14%	12%

N Engl J Med. 2016 Dec 1;375(22):2154-2164

NOVA Subgroups of Non-g*BRCA*mut Cohort

HRD-positive | **HRD-negative**

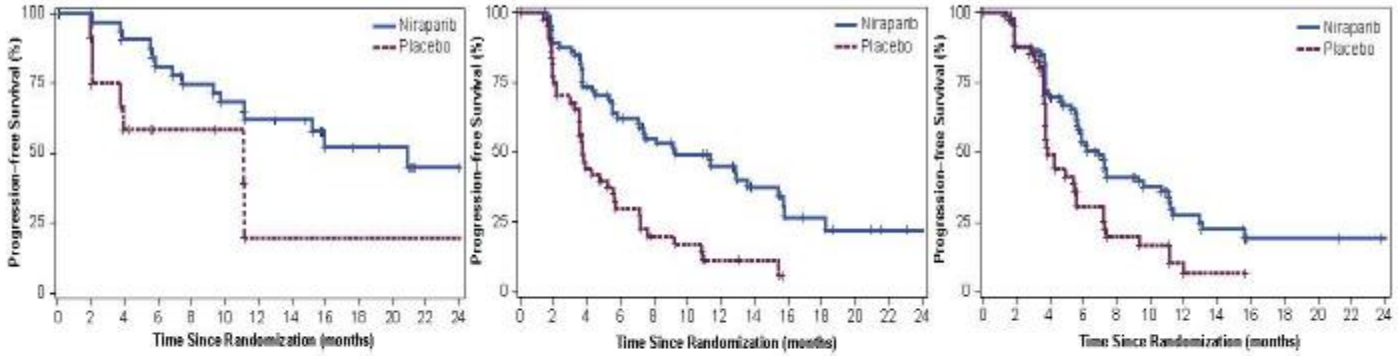
s*BRCA*mut

Treatment	PFS Median, months (95% CI)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (n=35)	20.9 (9.7, NR)	0.27 (0.081, 0.903) p=0.0248	62%	52%
Placebo (n=12)	11.0 (2.0, NR)		19%	19%

*BRCA*wt

Treatment	PFS Median, months (95% CI)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (n=71)	9.3 (5.8, 15.4)	0.38 (0.231, 0.628) p=0.0001	45%	27%
Placebo (n=44)	3.7 (3.3, 5.6)		11%	6%

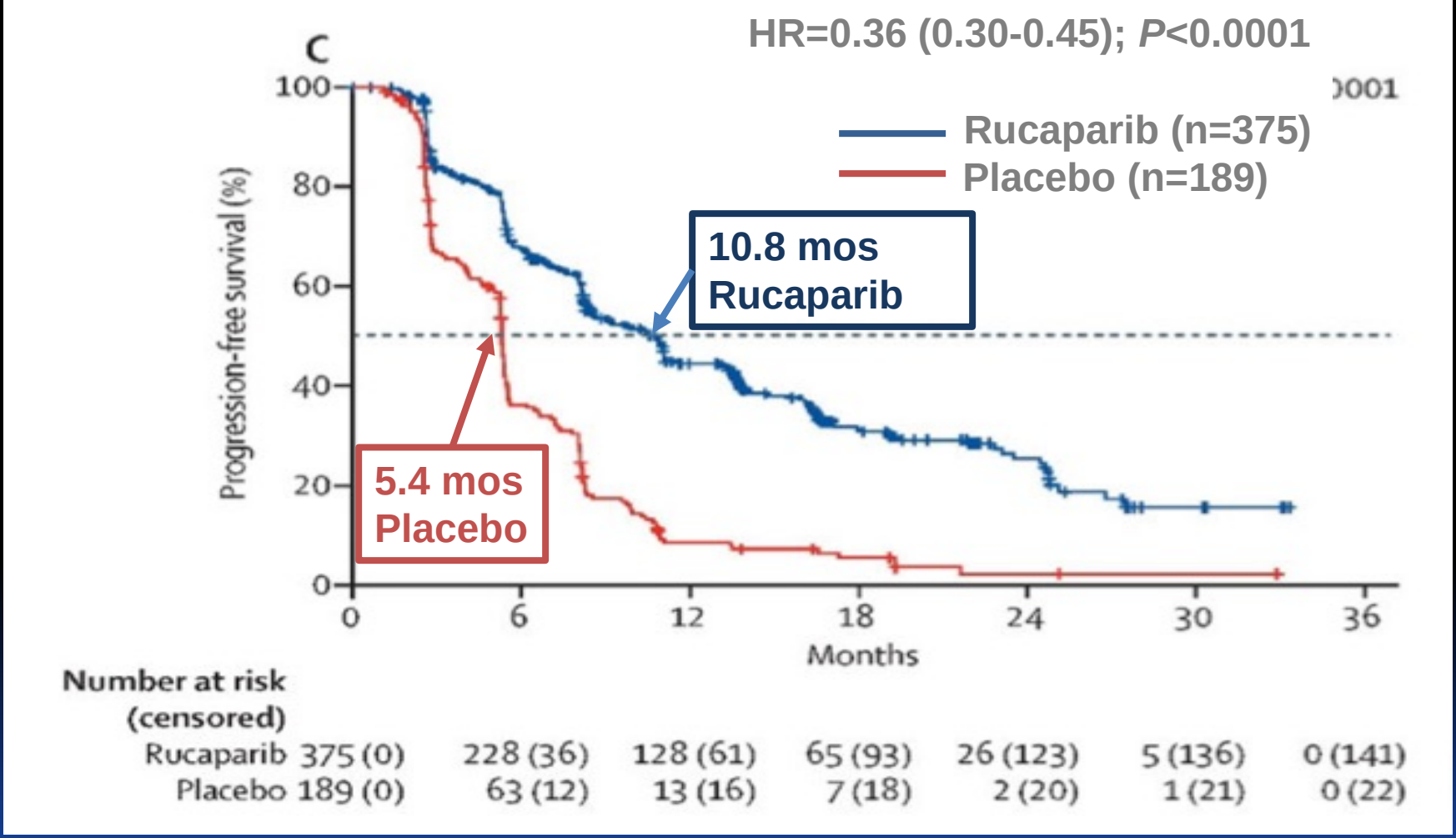
Treatment	PFS Median, months (95% CI)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (n=92)	6.9 (5.6, 9.6)	0.58 (0.361, 0.922) p=0.0226	27%	19%
Placebo (n=42)	3.8 (3.7, 5.6)		7%	7%



NR, Not reached.

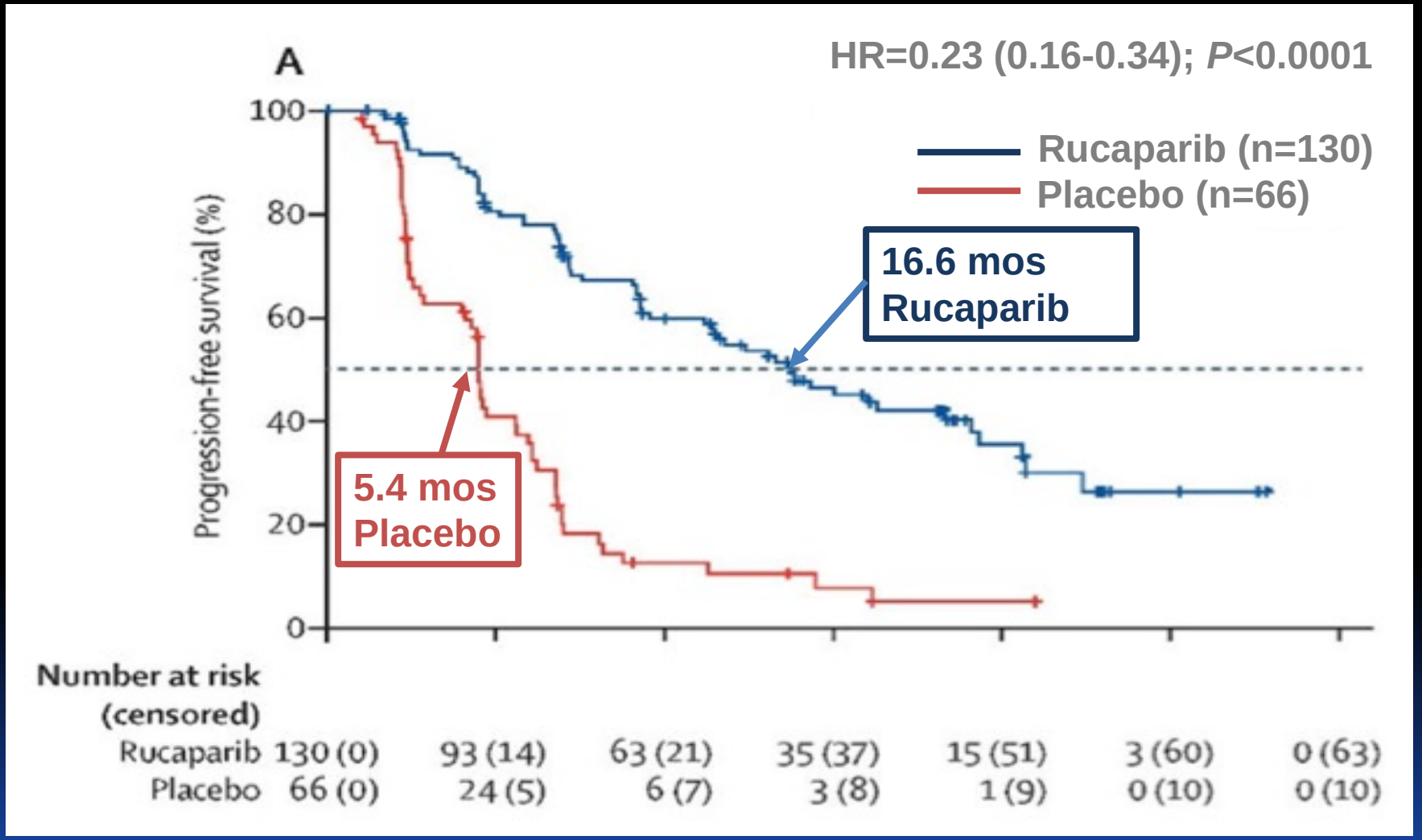
N Engl J Med. 2016 Dec 1;375(22):2154-2164

Ariel 3 PFS Regardless of *BRCA* Status



Coleman et al: Lancet 390:1949-1961, 2017

Ariel 3 PFS *BRCA*+ Patients

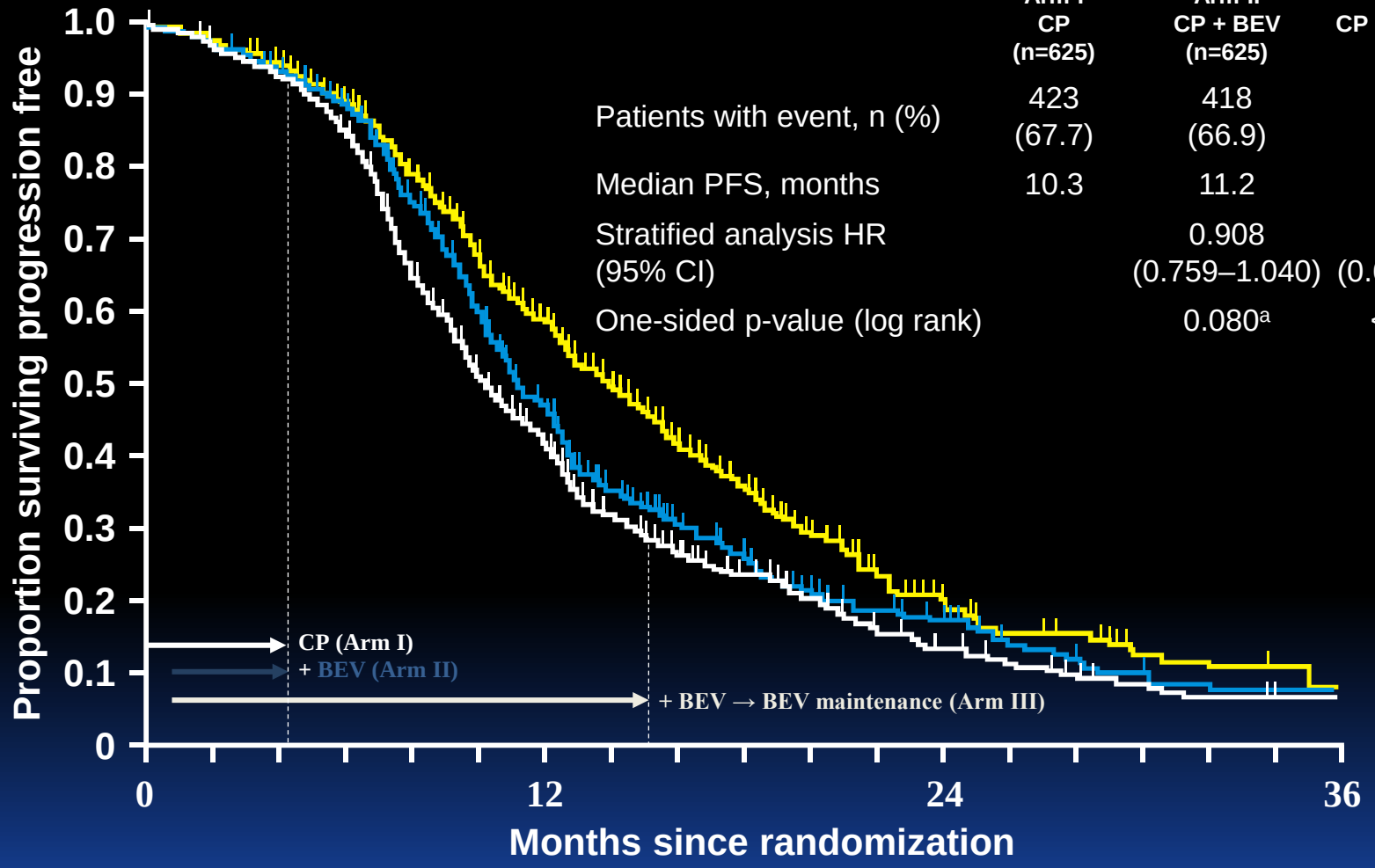


Coleman et al: Lancet 390:1949-1961, 2017

ARIEL 3 PFS by Mutation Subgroup

BRCA+	Events/Pts	Events/Pts	HR (CI)
BRCA1	48/80	29/37	0.32 (0.19-0.53)
BRCA2	19/50	27/29	0.12 (0.06-0.26)
Germline	47/82	42/48	0.25 (0.16-0.39)
Somatic	18/40	12/16	0.23 (0.10-0.54)
BRCA wild	**Events/Pts**	**Events/Pts**	**HR (CI)**
LOH high	67/106	45/52	0.44 (0.29-0.66)
LOH low	81/107	50/54	0.58 (0.40-0.85)
LOH indet	19/32	16/17	0.25 (0.11-0.56)

GOG-0218: PFS



	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
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)		0.080[a]	<0.0001[a]

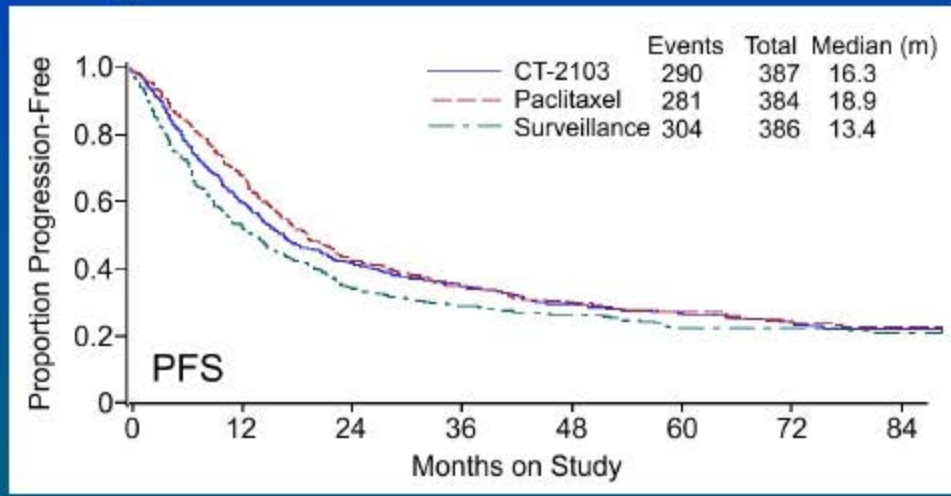
[a]p-value boundary = 0.0116

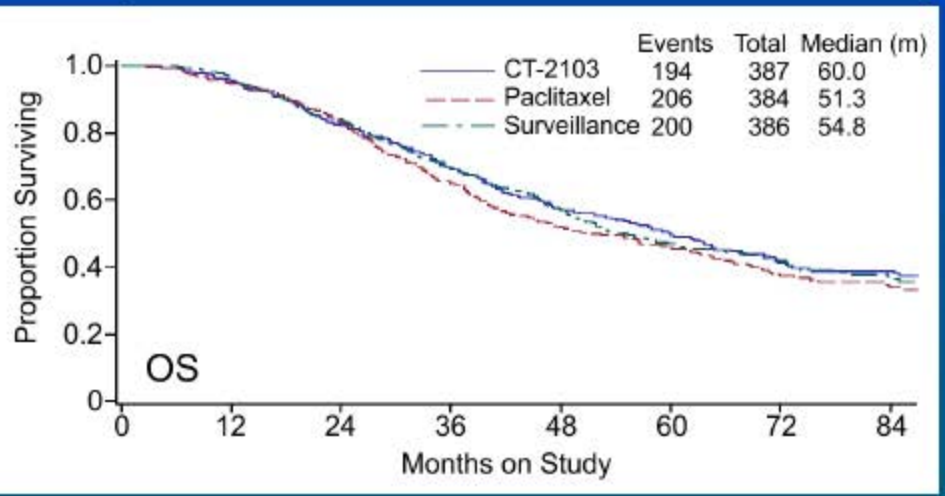
GOG212: Taxane Maintenance

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

	HR (97.5% CI)
CT-2103 vs OBS	0.847 (0.721 - 0.995)
Paclitaxel vs OBS	0.783 (0.783 - 0.921)

	HR (97.5% CI)
CT-2103 vs OBS	0.979 (0.781 - 1.23)
Paclitaxel vs OBS	1.104 (0.884 - 1.38)





Copeland L, et al. SGO 2017

Cost-Effectiveness of Maintenance Therapy in Advanced Ovarian Cancer
Paclitaxel, Bevacizumab, Niraparib, Olaparib, Rucaparib, and Pembrolizumab.

Juliet Wolford, MD[1], Jiaru Bai, PhD[3], Lindsey Minion, MD[1], Robin Keller, PhD[1], Ramez Eskander, MD[4], John Chan, MD[5], Bradley Monk, MD[6], Krishnansu Tewari, MD[1]

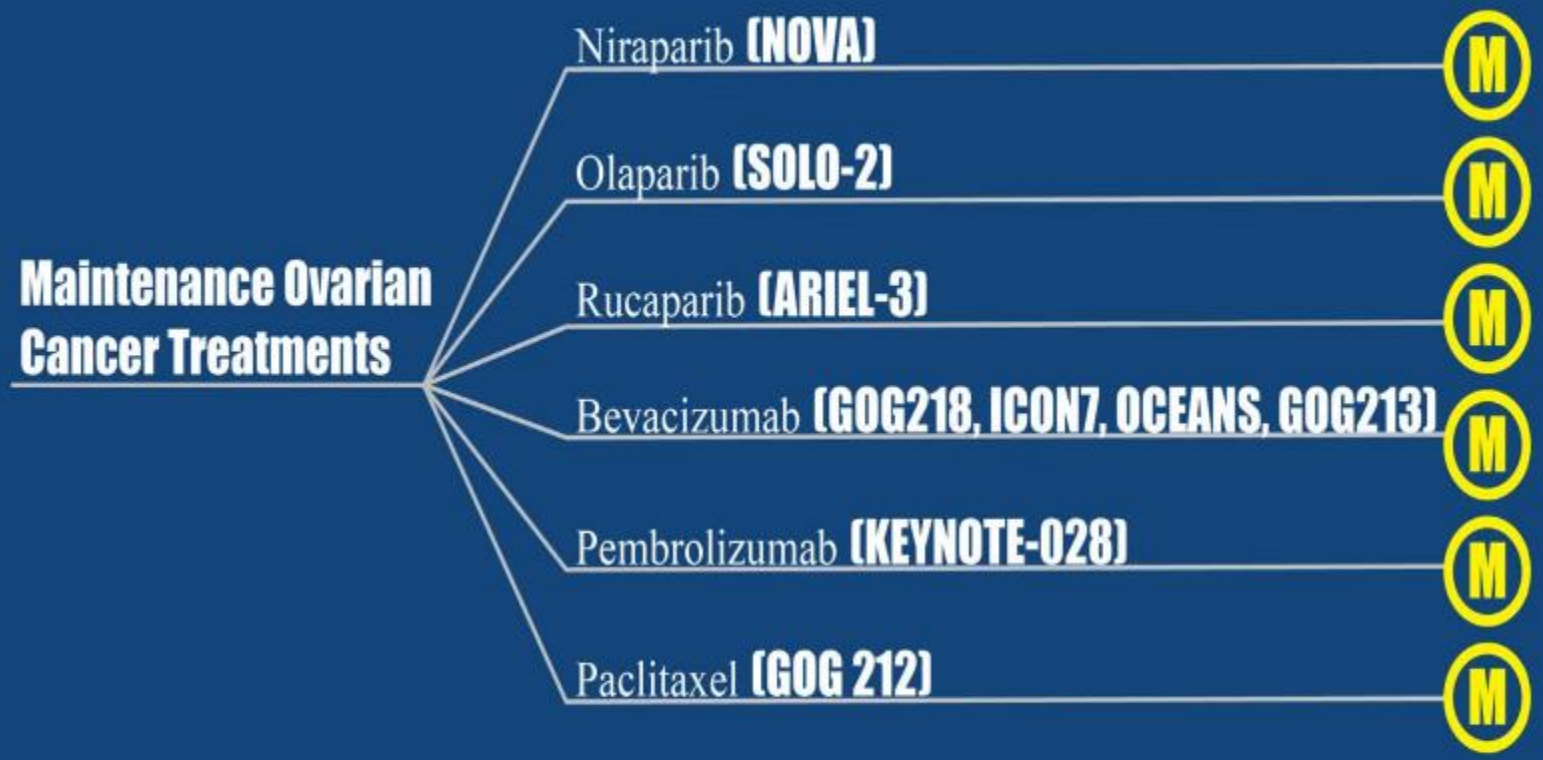
[1]School of Medicine and [2]Paul Merage School of Business, University of California
[3]School of Management, Binghamton University, State University of New York, Binghamton, NY
[4]University of California, San Diego, Moores Cancer Center, La Jolla, CA
[5]California Pacific Palo Alto Medical Foundation, Sutter Cancer Institute, San Francisco, CA
[6]Creighton University in Arizona at St. Joseph's Hospital & Medical Center, Phoenix, AZ

Presented By Juliet Wolford at 2018 ASCO Annual Meeting

Cost-Effective: What Does This Mean?

- Cost-effective published thresholds
  - $50,000 per quality-adjusted life-year (QALY)
  - Range between $20,000 and $100.000/QALY more recently
  - WHO: 3X per capita GDP per country (US = $150,000/QALY
- Problems with invoking thresholds
  - Purports to establish the value of human life
  - Assumes consensus
  - Implies central control with a fixed budget

METHODS : Registration Trials

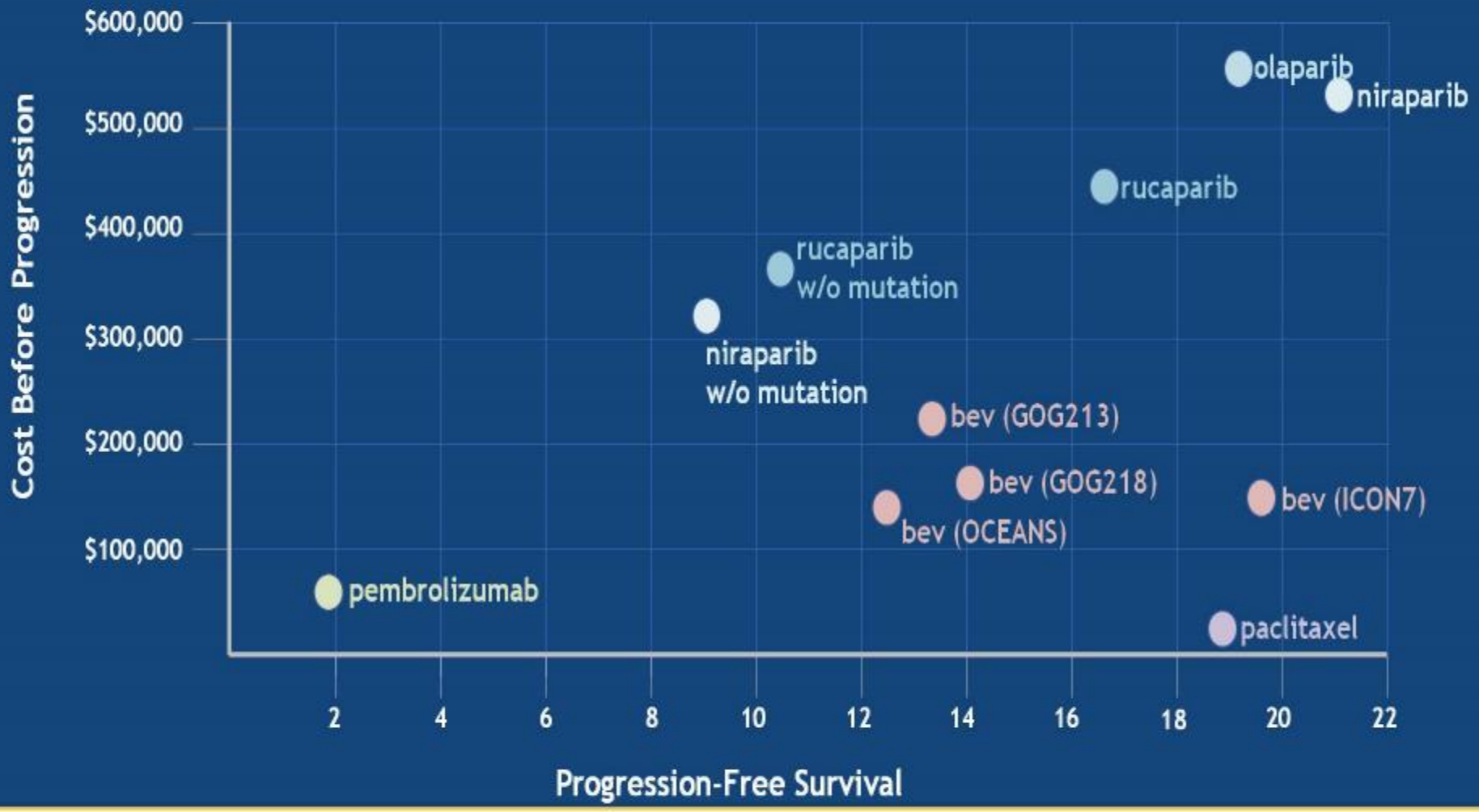


METHODS : Determining the Costs

Estimated Cost Breakdown

	Drug	Study	Dose	Drug Cost	Pre-Tx Cost	Infusion Cost	Heme Tox Cost	Non-Heme Tox	Combined Cost per Drug
PARPi	Niraparib	*NOVA*	300mg QD	17,700.00	3351.85	0.00	1187.52	5572.83	**$27,812.21**
	Olaparib	*SOLO 2*	300mg BID	16,178.40	3351.85	0.00	925.04	2033.28	**$22,488.57**
	Rucaparib	*ARIEL 3*	600mg BID	16,488.00	3048.85	0.00	965.58	5896.68	**$26,399.10**
Anti-Angio	Bevacizumab	*GOG 218*	15mg/kg q 3 weeks	9,557.63	197.11	568.13	1478.66	3173.13	**$14,974.66**
	Bevacizumab	*ICON 7*	7.5mg/kg q 3 weeks	4,778.82	197.11	568.13	1511.69	5998.73	**$13,054.48**
	Bevacizumab	*OCEANS*	15mg/kg q 3 weeks	9,557.63	197.11	568.13	2981.77	2845.84	**$16,150.48**
	Bevacizumab	*GOG 213*	15mg/kg q 3 weeks	9,557.63	197.11	568.13	1518.85	4952.85	**$16,794.57**
Immuno	Pembrolizumab	*KEYNOTE 028*	200mg q 3 weeks	10,994.20	1266.65	568.13	0.00	2820.83	**$15,649.81**
Chemo	Taxol	*GOG 212*	175mg/m2 q monthly	152.76	94.81	568.13	577.50	3524.81	**$4,918.01**

RESULTS: Cost Effectiveness → Cost vs PFS



METHODS: ICER Calculation

$$\text{ICER} = \frac{\text{Cost of Drug A- Cost of Drug B}}{\text{PFS of Drug A- PFS of Drug B}}$$

RESULTS: QALmonth

	Costs: (Expected cost)	QALmonth before progress(Expected Months)	Cost-Effectiveness	ICER of Niraparib with mutation	ICER of Olaparib	ICER of Rucaparib with no mutation	ICER of Bevacizumab (OCEANS)	ICER of Taxol	ICER of Pembrolizumab
Treatment	*Cost before next line*	*PFS*	*vs PFS*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*
Niraparib with mutation	$515,211	16.8	$30,759				$30,759	dominated by Taxol	$34,538
Olaparib	$564,451	19.0	$29,708				$29,708	dominated by Taxol	$32,640
Rucaparib with mutation	$451,499	16.0	$28,219				$28,219	dominated by Taxol	$31,387
Bev (GOG218)	$177,750	12.3	$14,510	$74,991	$57,289	$73,000		dominated by Taxol	$12,472
Bev (ICON7)	$175,660	21.8	$8,076	dominated by Bev (ICON7)	dominated by Bev (ICON7)	dominated by Bev (ICON7)		$54,741	$5,679
Bev (OCEANS)	$172,752	11.8	$14,702	$68,492	$54,027	$65,587		dominated by Taxol	$12,632
Bev (GOG213)	$217,882	14.0	$15,563	$108,120	$69,314	$116,809		dominated by Taxol	$14,303
Taxol	$25,123	19.0	$1,322	dominated by Taxol	dominated by Taxol	dominated by Taxol	dominated by Taxol		dominated by Taxol
Pembrolizumab	$74,853	4.0	$18,713	$34,538	$32,640	$31,387	$18,713	dominated by Taxol	

Maintenance Therapy

ASCO 5508: Cost Effectiveness

Drug	PFS	Cost/PFSyr
Olaparib	19.1 mos	$356,496
Niraparib	21.0 mos	$369,108
Rucaparib	16.6 mos	$338,628
Bevacizumab	14.1 mos	$186,756

Maintenance Therapy

SGO 16: Cost Effectiveness in PSOC

Drug	gBRCA		Non-gBRCA		HRD	
	PFS Diff	ICER	PFS Diff	ICER	PFS Diff	ICER
Olaparib	13.6 mo	$231,567				
Niraparib	15.5 mo	$244,322	3.1 mo	$304,775	9.1 mo	$255,609
Rucaparib	11.2 mo	$248,992			8.2 mo	$278,552
Bevacizumab			4.0 mo	$531,151		

ICER = incremental cost effectiveness ratio expressed as cost/PF-LYS where PF-LYS = progression-free life year saved
PFS diff = difference between control and experimental arms in mos

Maintenance Therapy

SGO 19: Foot et al

- **ASCO Net Health Benefit (NHB) and ESMO Magnitude of Clinical Benefit Scale (MCBS)**
- **Scores were highest in women with germline or somatic BRCA mutations and tumor HRD positivity**
- **Scores for non-biomarker positive patients similar to results with bevacizumab**
- **Cost not a part of this trial**

Maintenance Therapy

Bottom Line

- **The clinical benefit of maintenance therapy in epithelial ovarian cancer is clear.**
- **Valid maintenance options include: PARPi, anti-angiogenic therapy, paclitaxel**
- **While the cost of PARPi maintenance is greater than certain other options, the cost effectiveness can be enhanced by:**
  - **Selective treatment of those with BRCA/HRD**
  - **More accurate determination of optimal dose**
  - **Competition in the market place**
- **Absolute magnitude of benefit independent of cost appears to be greatest with PARPi, particularly in patients with HRR deficiency.**

Maintenance Therapy

So What Should We Do? (one opinion)

- Maintenance therapy should be offered in PSOC with clinical benefit from induction.
  - BRCA+, HRD+ patients: PARPi
  - Patients without BRCA or HRD: either PARPi or bevacizumab
- Maintenance therapy should be offered in front-line patients with clinical benefit from induction.
  - Bevacizumab for now
  - Role of PARPi awaits front-line studies
- Taxanes can be considered

Gynecologic Cancer

Discussion Topics

- Ovarian Cancer
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506
- Cervical Cancer
  - Neoadjuvant Chemotherapy: ASCO 5523
- Uterine Cancer
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505

Ovarian Carcinoma

Role of Bevacizumab

- Bevacizumab active against ovarian carcinoma.
  - Based on 3 phase II trials
  - Induces responses, prolonged PFS
- Bevacizumab added to chemotherapy improves PFS in ovarian cancer.
  - 5 phase III trials (2 front-line, 3 recurrent disease)
  - Maintenance bevacizumab critical to success
- Hypertension only significantly increased toxicity across all five trials.
- FDA-approved in platinum-resistant and platinum-sensitive disease as well as newly diagnosed advanced diseased

Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Sandro Pignata

Ovarian Carcinoma

MITO16B – MaNGO OV2B – ENGOT OV17

- Stages III-IV in first relapse
- PFI ≥6 mos
- PS 0-2
- RECIST progression +/- measurable disease
- Normal organ function
- Tumor samples for molecular analysis

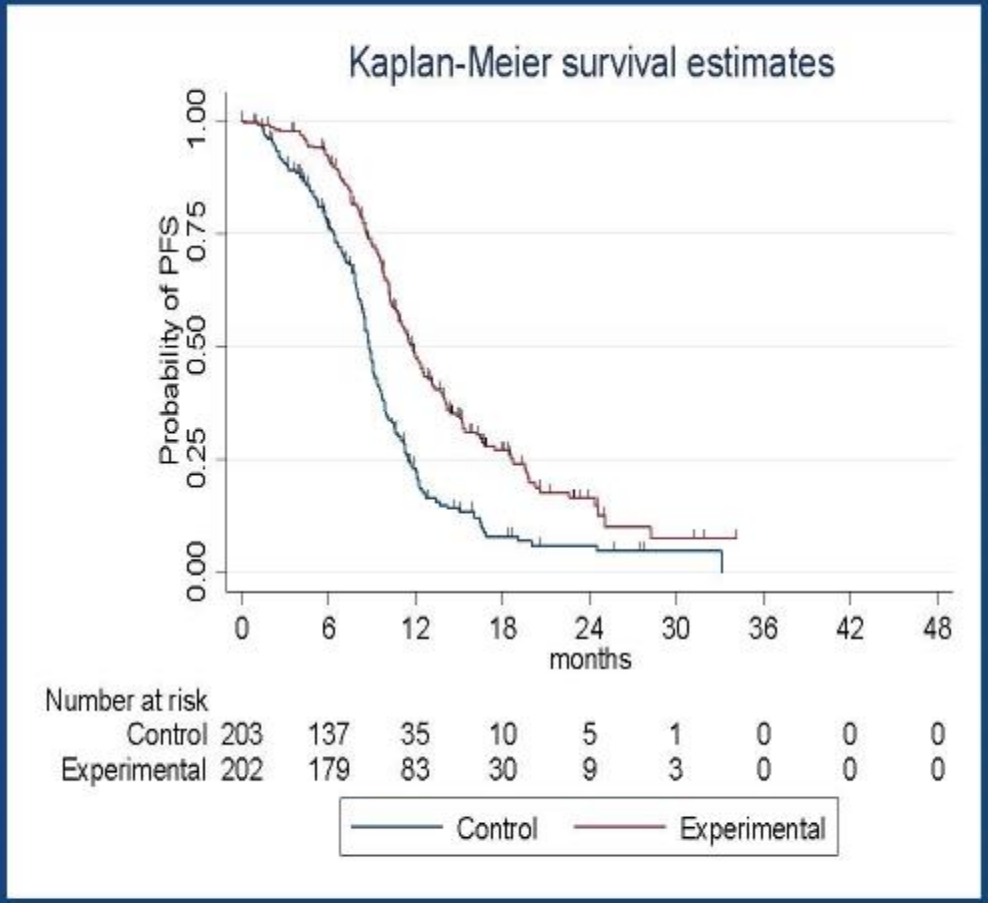
RANDOMIZE

→ Platinum-Based Chemotherapy

→ Chemotherapy plus Bevacizumab
Bevacizumab Maintenance

- Primary Endpoint: PFS
- Expected PFS: 8 v 11.9 mos
- Hazard Ratio: 0,67
- Patients: 400 (265 events)

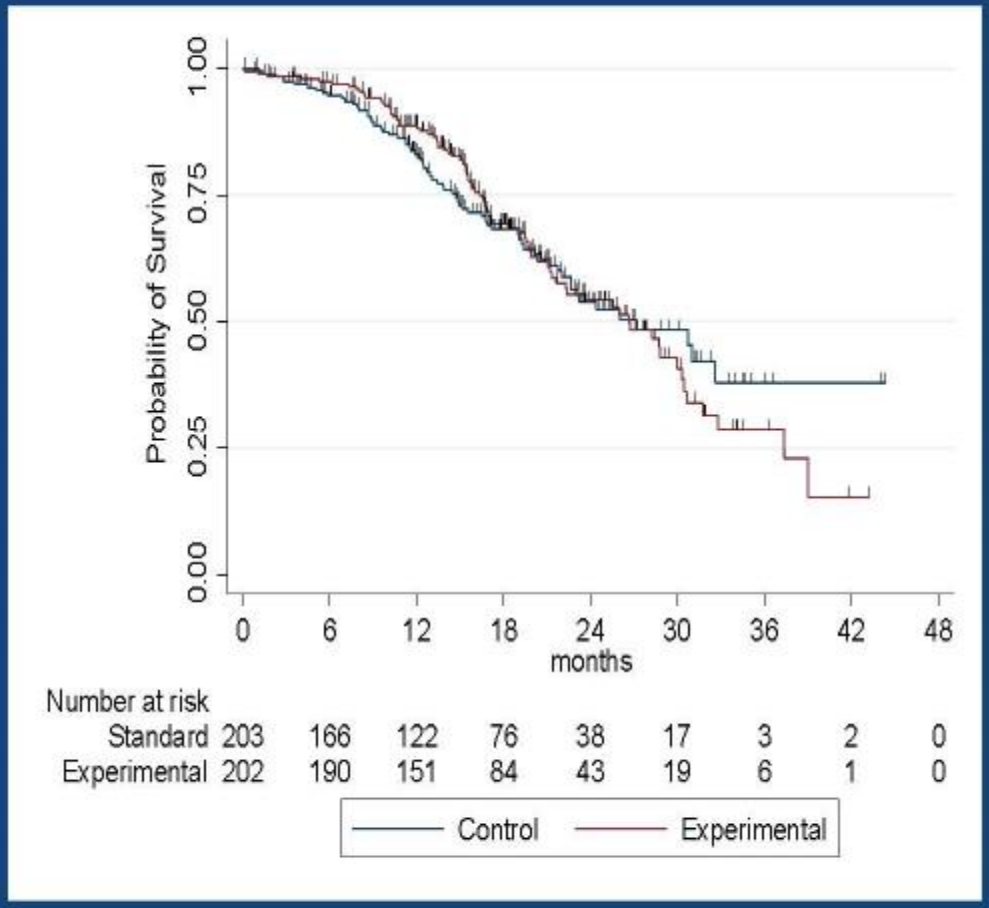
PFS Investigator assessed (primary end-point)



	Standard	Experimental	Log Rank P
# events	161	143	
Median PFS	8.8 mos	11.8 mos	<0.001
HR* (95%CI)	0.51 (0.41-0.65)		

*adjusted by:
age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Overall survival



	Standard	Experimental	
	Chemo	Chemo/Bev	Log Rank P
Event	68	79	
Med OS	27.1 mo	26.6 mo	0.98
HR (95% CI)			0.97 (.70-1.35)

Adjusted by:
Age, PS, center size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Bev after Bev: Response

	Chemo	Chemo/Bev	P
Patients	143	130	
Responders	94 (65.7%)	97 (74.6%)	0.14
CR	9 (6.3%)	20 (15.4%)	
PR	85 (59.4%)	77 (59.2%)	

Severe Toxicity occurring >4% of patients

	STD (N=200)		EXP (N=201)		
	G3	G4	G3	G4	P*
Hypertension	20 (10%)	0	58 (28.9%)	0	<0.001
Neutrophils	56 (28%)	25 (12.5%)	48 (23.9%)	32 (15.9%)	0.95
Thrombocytopenia	20 (10%)	23 (11.5%)	31 (15.4%)	30 (14.9%)	0.04
Proteinuria	0	0	8 (3.9)	0	0.007
Febrile Neutropenia	6 (3%)	4 (2%)	3 (1.5%)	1(0.5%)	0.17
Allergic Reaction	11 (5.5%)	0	5 (2.48%)	1 (0.5%)	0.22
Anemia	22 (11%)	1(0.5%)	22 (10.9%)	0	0,88

*Chi-square or Fisher's exact test as appropriate (severe vs non-severe)

Ovarian Carcinoma: Bev after Bev

Conclusions

- Rechallenging PSOC with a platinum-based doublet plus bev significantly prolongs PFS with no unexpected toxicities
- Rechallenging with bev is an option in recurrent patients previously exposed to bev

Gynecologic Cancer

Discussion Topics

- Ovarian Cancer
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506
- Cervical Cancer
  - Neoadjuvant Chemotherapy: ASCO 5523
- Uterine Cancer
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505

Neoadjuvant Chemotherapy with Cisplatin and Gemcitabine followed by Chemoradiation with Cisplatin in Locally Advanced Cervical Cancer: a Phase II, Prospective, Randomized, Trial

- Samantha Silva, Renata R. C. Colombo Bonadio, Flavia Gabrielli, Andrea Souza Aranha, Maria Luiza Genta, Vanessa Costa Miranda, Daniela Freitas, Elias Abdo Filho, Patricia Alves De Oliveira Ferreira, Karime Kalil, Mariana Scaranti, Maria Del Pilar Estevez-Diz
- Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil

Presented By Don Dizon at 2018 ASCO Annual Meeting

Is there a role for NACT?

2003 Meta-Analysis (n=21 RCT)

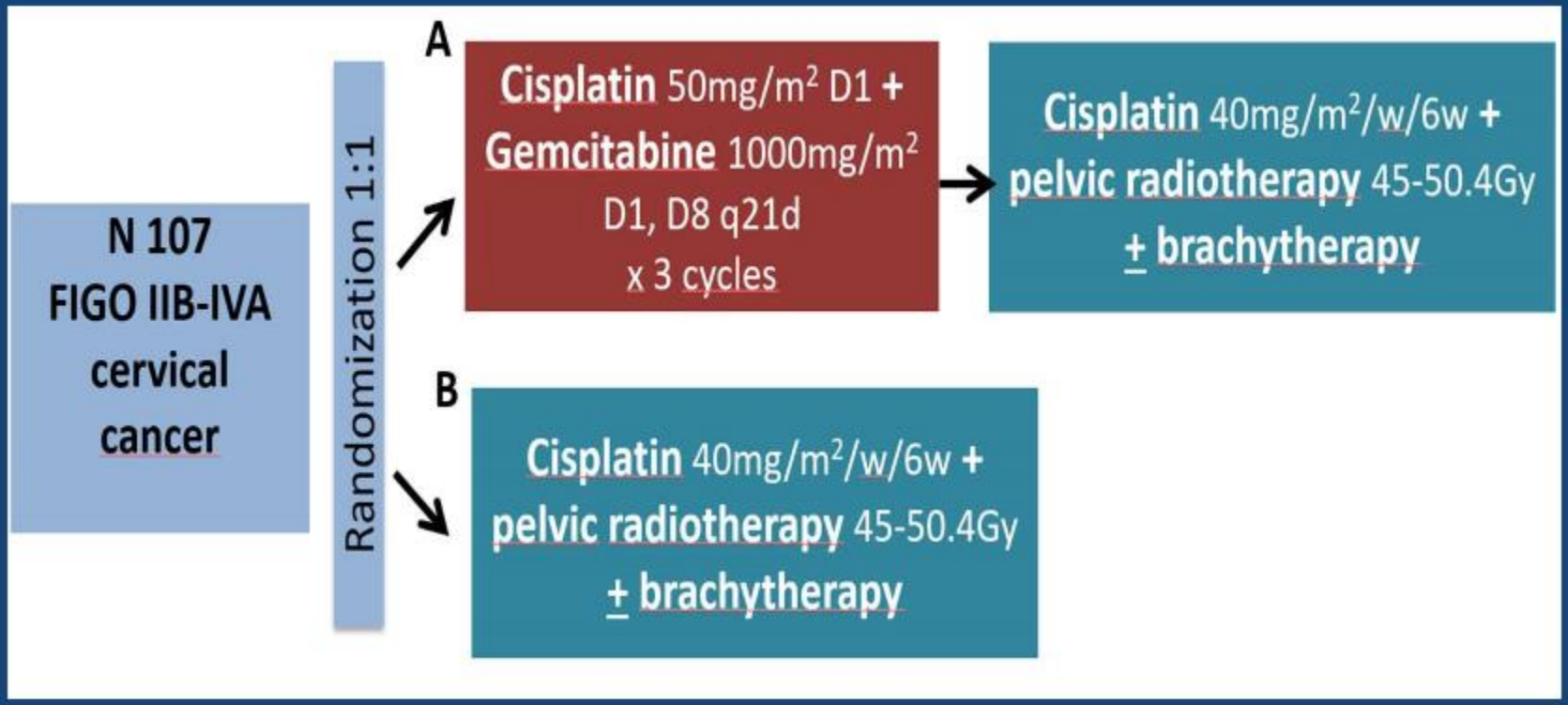
Compared to RT alone, NACT followed by RT:

- Benefit in OS if chemotherapy given ≤14 days (HR 0.83, 95%CI 0.69-1.0)
- Benefit in OS if cisplatin dose ≥25 mg/m2 (HR 0.91, 95%CI 0.78-2.05)
- **Detrimental to OS if one or other not met**

Compared to RT alone, NACT followed by surgery:

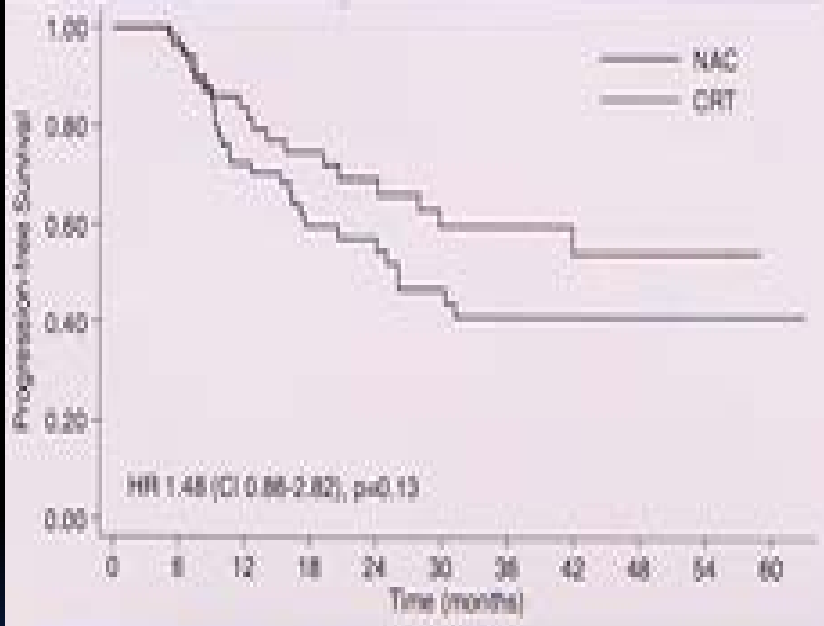
- Benefit in OS (HR 0.65, 95%CI 0.53-0.80)

Is there a role for NACT?



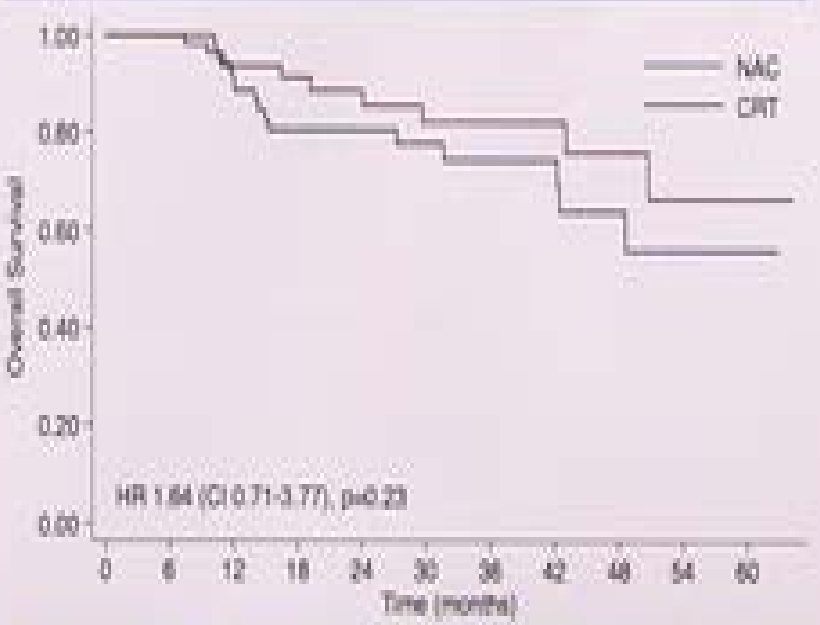
Results: PFS and OS

Figure 1. Kaplan-Meier curves for PFS



	NAC	CRT	HR	CI 95%	p
3y-PFS	41.1%	59.6%	1.48	0.86-2.82	0.134

Figure 2. Kaplan-Meier curves for OS



	NAC	CRT	HR	CI 95%	p
3y-OS	74.2%	81.9%	1.64	0.71-3.77	0.230

Cervix Carcinoma: NACT v CCRT

NACT: Summary and Conclusions

- No difference in 3-year PFS and OS with the addition of NACT to CCRT for stages IIB-IVA
- CR rate with NACT inferior to CCRT
- Toxicities
  - Acute toxicities more frequent with NACT
  - No differences in late toxicities
- Bottom line: CCRT without NACT remains the standard of care

Gynecologic Cancer

Discussion Topics

- Ovarian Cancer
  - Surgery: ASCO 5500, SGO 43; HIPEC; ASCO 5501
  - PARPs and Maintenance Therapy: ASCO 5508, Aghajanian, Tian; SGO 16, 19, 21
  - Bevacizumab: Overview; ASCO 5506
- Cervical Cancer
  - Neoadjuvant Chemotherapy: ASCO 5523
- Uterine Cancer
  - Papillary Serous: SGO 22
  - Leiomyosarcoma: ASCO 5505

Uterine Papillary Serous Carcinoma

UPSC: Basic Facts

- 10-20% of endometrial carcinomas
- More aggressive, spreads early often with intraperitoneal dissemination
- Reported to account for as much as 50% of EC relapses and 40% of EC-related deaths
- GOG 177:
  - 61% HER2 overexpression (2+ or 3+) by IHC
  - 21% FISH positive (n=38)

Trastuzumab in UPSC

Population	Patients	PFS PC	PFS PCT	HR (CI)	P value
All	58	8.0 mos	17.6 mos	0.44 (0,26-0,76)	0.005
Stage III-IV	41	9.3 mos	17.9 mos	0.40 (0.20-0.80)	0.013
Recurrent	17	6.0 mos	9.2 mos	0.14 (0.04-0.53)	0.003

- **Santin et al SGO 22**
- **All patients overexpress HER2/neu.**
- **Randomization to Paclitaxel/Carboplatin +/- Trastuzumab (6 cycles PC, trastuzumab to progression or unacceptable toxicity).**

Gynecologic Cancer

Discussion Topics

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Adjuvant Gemcitabine plus Docetaxel followed by Doxorubicin versus Observation for Uterus-Limited, High Grade Leiomyosarcoma: a Phase III NRG Oncology/Gynecologic Oncology Group Study

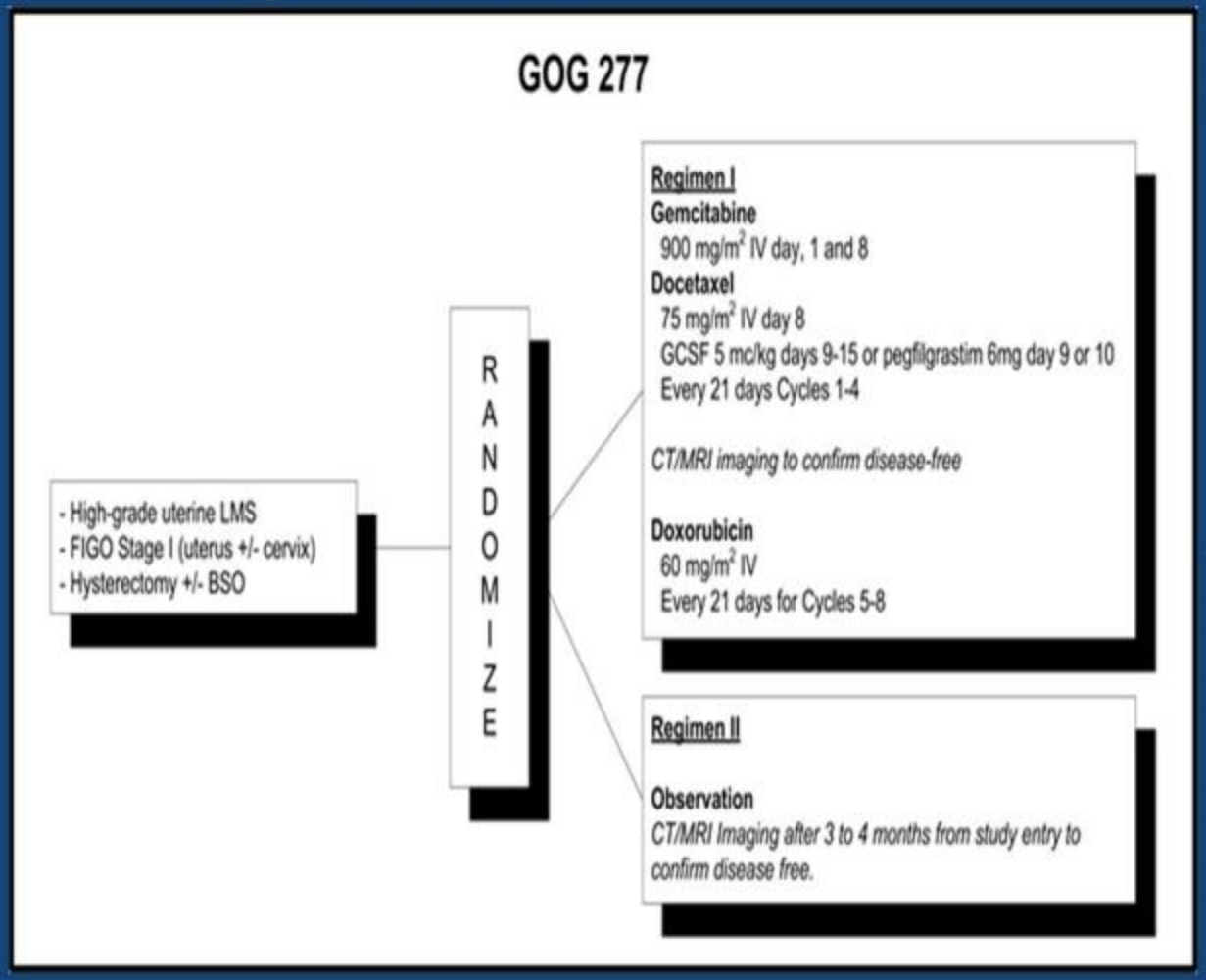
Martee L. Hensley MD, Danielle Enserro PhD, Helen Hatcher PhD, Petronella B. Ottevanger MD PhD, Anders Krarup-Hansen MD PhD, Jean-Yves Blay MD PhD, Cyril Fisher MD, DSc, Katherine M. Moxley MD, Shashikant B. Lele MD, Jayanthi S. Lea MD, Krishnansu S. Tewari MD, Premal Thaker MD, Oliver Zivanovic MD, David M. O'Malley MD, Katina Robison MD, David S. Miller MD, FACS

Uterine Leiomyosarcoma

Leiomyosarcoma: Basic Facts

- High-grade uterine LMS completely resected: 50-70% risk of recurrence
- Neither radiotherapy nor chemotherapy shown to derease recurrence rate or improve survival
- Gemcitabine-docetaxel and doxorubicin active in metastatic LMS
- SARC005: phase II study of adjuvant gem-doc:
  - 46% recurrence rate
  - 57% disease-free at 3 years

Study Schema



- CT CAP or CT chest + MR a/p prior to randomization to confirm NED
- CT CAP or CT chest + MR a/p every 4 months for 3 years, then every 6 months for 2 years

GOG 277: Results

	Observation	Chemotherapy	95% CI
Patients	16	20	
Recurrences	8	8	
RFS	14.6 mos	18.1 mos	-2.4 to 9.3 mos
OS	46.4 mos	34.3 mos	-21.5 to -2.7 mos

Leiomyosarcoma

GOG 277: Summary and Conclusions

- Closed early due to slow accrual
- Study endpoints
  - 47% of patients on chemo had at least one G 3-4 event
  - RFS with chemo numerically but not statistically better by 3.4 mos (could be worse by 2.4 mos or better by 9.3 mos)
  - OS worse with chemo by 12.1 mos (-21.5 mos to -2.7 mos)
- OS does not include possibility that survival might be better with chemo
- Bottom line: observation following complete, intact resection of uterus-limited high-grade LMS remains the standard of care

Gynecologic Cancer

Discussion Topics

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Gynecologic Cancer

What Have We Learned in 2017-2018?

- Ovarian Cancer
  - **Surgery: front-line debulking**
    - PDS and NACT yield similar results overall.
    - The goal of debulking is R0 with hints that R0 debulking by PDS Is more meaningful than R0 by IDS after NACT.
    - NACT may have an advantage in patients in poor condition.
  - **Surgery: IDS +/- HIPEC**
    - HIPEC at time of IDS improves PFS, OS
    - Trial needs confirmation and to address caveats
  - **Surgery: secondary surgical debulking**
    - Debulking in this setting achieved R0 status in 68% of patients, similar to 72% in the DESKTOP-III trial.
    - Unlike the DESKTOP-III trial, there was no significant PFS or OS advantage to debulking; the difference may be bevacizumab.

Gynecologic Cancer

What Have We Learned in 2017-2018?

- Ovarian Cancer
  - PARP inhibitors
    - Three PARP inhibitors are available for ovarian carcinoma.
      - Third line or greater as single agent treatment
      - Maintenance therapy for patients who achieve a CR or PR to second or subsequent platinum-based therapy in PSOC
    - Markers of homologous recombination repair deficiency (BRCA or HRD) identify those most likely to respond.
  - Maintenance therapy in ovarian carcinoma responders
    - Maintenance options with evidence demonstrating benefit include: PARPi, anti-VEGF therapy, and paclitaxel.
    - Greatest clinical benefit is associated with PARPi.
    - By current proposed standards ($100,000/PFQALY), only paclitaxel is considered cost effective.
    - In my opinion, PARPi, bevacizumab, and paclitaxel should be considered for all patients with CR, PR, or SD.

Gynecologic Cancer

What Have We Learned in 2017-2018?

- Ovarian Cancer
  - **Bevacizumab after bevacizumab** improves PFS and possibly eliminates the need for secondary surgical debulking.
- Cervical Cancer
  - **Neoadjuvant Chemotherapy (**gemcitabine/cisplatin) followed by CCR yields inferior PFS/OS/CR rate with greater toxicity.
- Uterine Cancer
  - **Papillary Serous**: Patients with HER2+ UPSC show significantly improved PFS/OS with PC plus trastuzumab.
  - **Uterine leiomyosarcoma**
    - Observation following complete, intact resection of uterus-limited high-grade LMS remains the standard of care