



Gynoncologica ASCO 2018, Chicago

Roy Lalisang, MUMC+



POST—ASCO



Oncologisch Netwerk
Zuidoost-Nederland

Disclosure

(potentiële) belangenverstrengeling	geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	geen
<ul style="list-style-type: none">• Sponsoring of onderzoeksgeld• Honorarium of andere (financiële) vergoeding• Aandeelhouder• Andere relatie, namelijk ...	<ul style="list-style-type: none">• geen• geen• nvt• nvt

Vogelvlucht

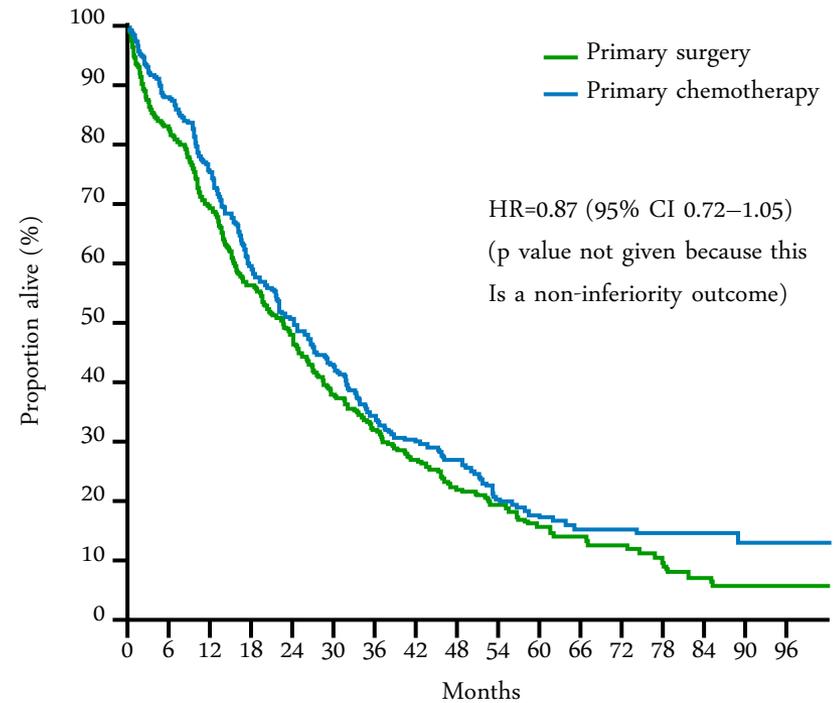
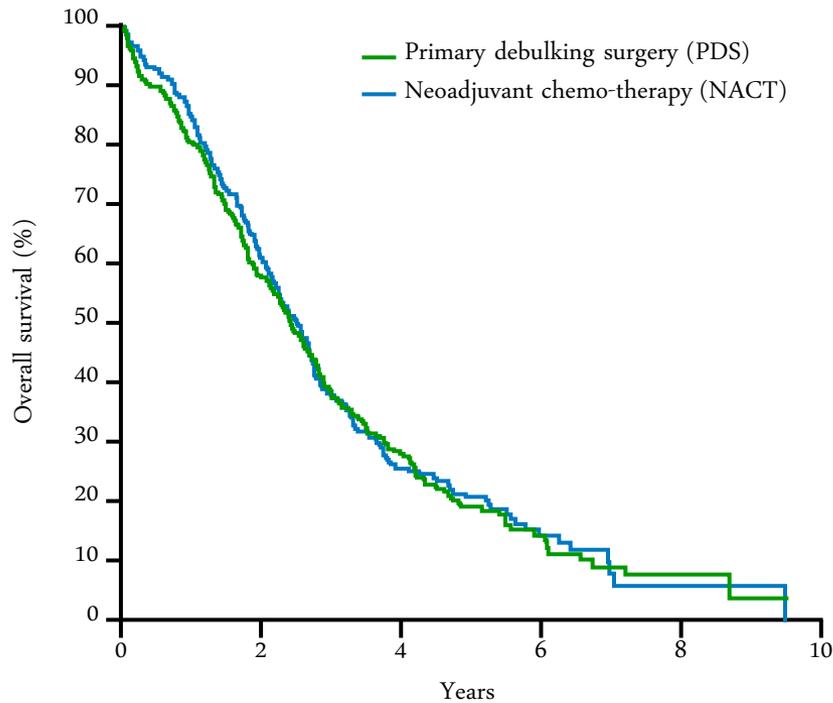
- ✓ PDS vs NACT in gevorderd ovariumcarcinoom “NACT de nieuwe standaard”?
- ✓ Secundaire debulking bij 1^{ste} platinum gevoelig recidief ovariumcarcinoom “Na DESKTOP III alles duidelijk”?
- ✓ Minimaal invasieve chirurgie bij vroegstadium cervixcarcinoom “Quo Vadis”?
- ✓ Kosten van onderhoudstherapie bij het ovariumcarcinoom “The financial burden”!

Design of the two phase III trials addressing NACT

EORTC 55971¹

CHORUS²

Intention-to-treat analysis



	No. of events		Number of patients at risk			
PDS	253	336	189	62	14	2
NACT	245	334	195	46	13	2

	Number at risk										
Primary surgery	276	225	189	153	128	83	51	22	17	6	3
Primary chemotherapy	274	239	205	161	137	88	59	31	21	14	3

*Definition of successful surgery: maximum effort for complete resection of visible tumour

1. Vergote, et al. NEJM 2010; 2. Kehoe, et al. Lancet 2015

PDS vs NACT, 3^{de} RCT



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

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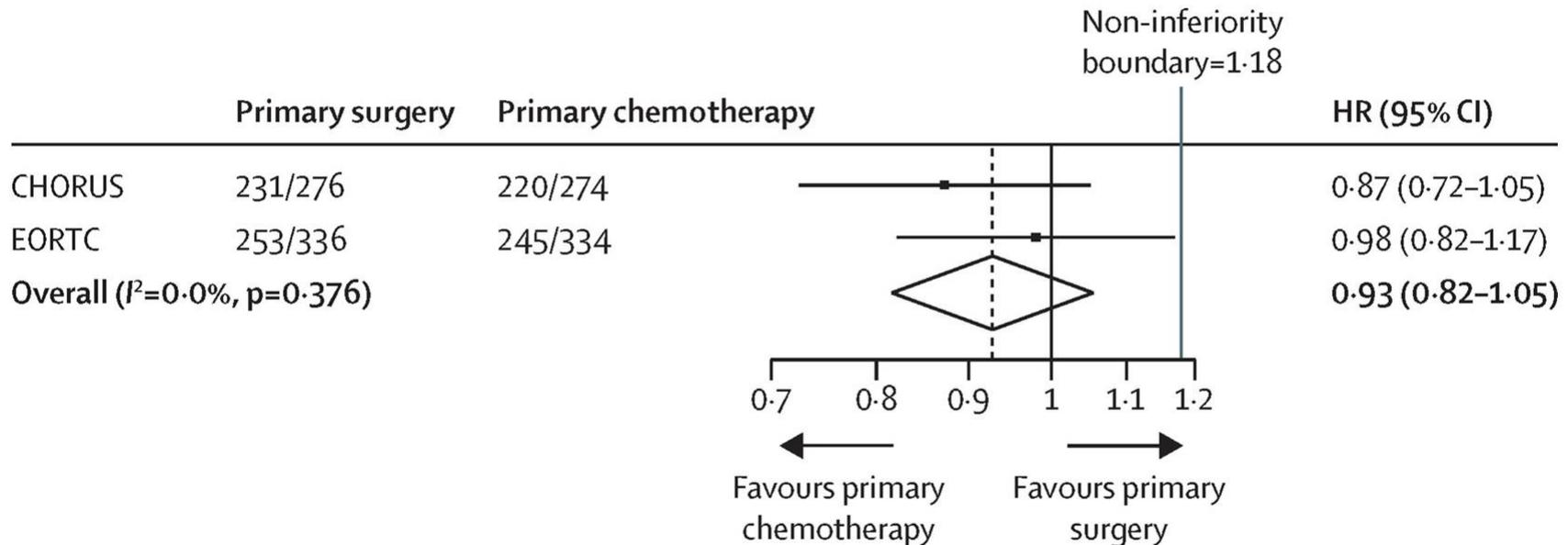
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Randomized Trials: PDS vs NACT



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Kehoe, S et al. Lancet, 386:249-257, 2015
Vergote, I et al. NEJM, 363:943-953, 2010

Trial Design

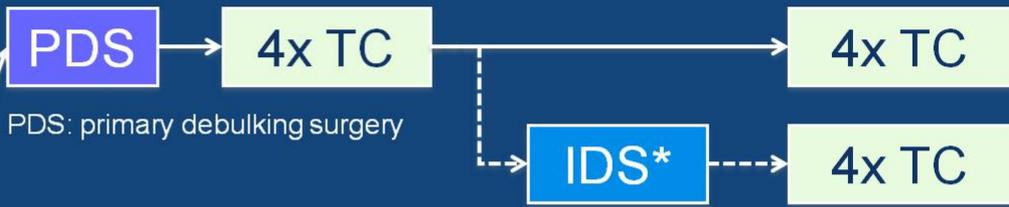
Multicenter (34 specialized institutions),
Randomized Phase III Trial

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

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

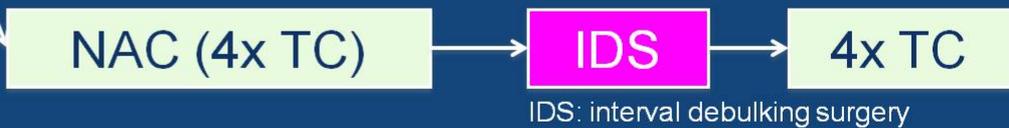
R
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Standard Arm (PDST)



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

Experimental Arm (NACT)



TC regimen: PTX 175 mg/m² iv, CBDCAAUC 6.0 iv

Main Objective of the JCOG0602

- To prove non-inferiority of NACT compared with PDST in terms of OS.
- Primary Endpoint
Overall Survival (OS)
- Secondary Endpoint
Progression-free Survival (PFS)

Initial Statistical Considerations

Planned sample size was 300

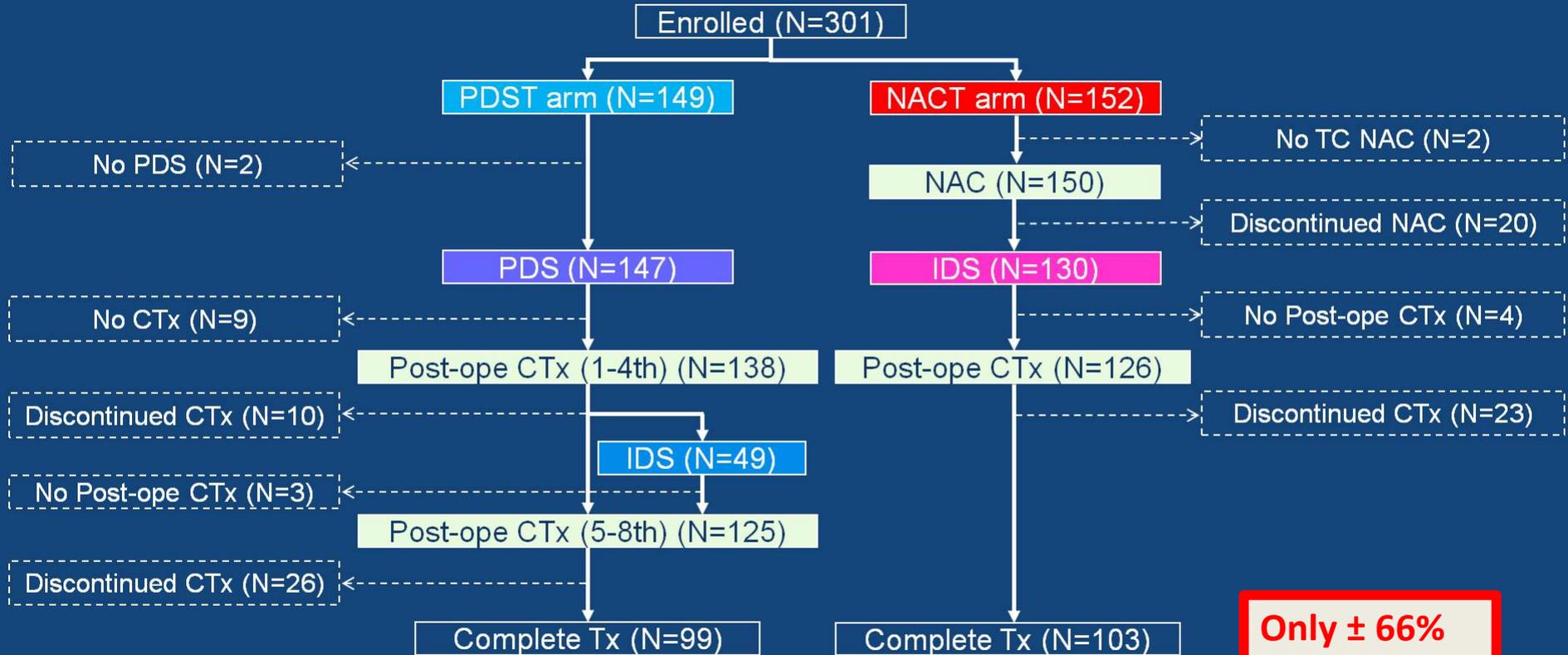
(Expected number of events was 276)

- 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

Revised Statistical Considerations

- Accrual period was extended to nearly 5 years
- Follow-up period was extended to 6 years due to fewer events
- Final number of events was 227, power was 0.73
- Interim analysis was performed twice
 - Predetermined analysis and additional analysis due to the extension of study period
 - Multiplicity adjusted alpha = 0.04598

CONSORT Flow Diagram



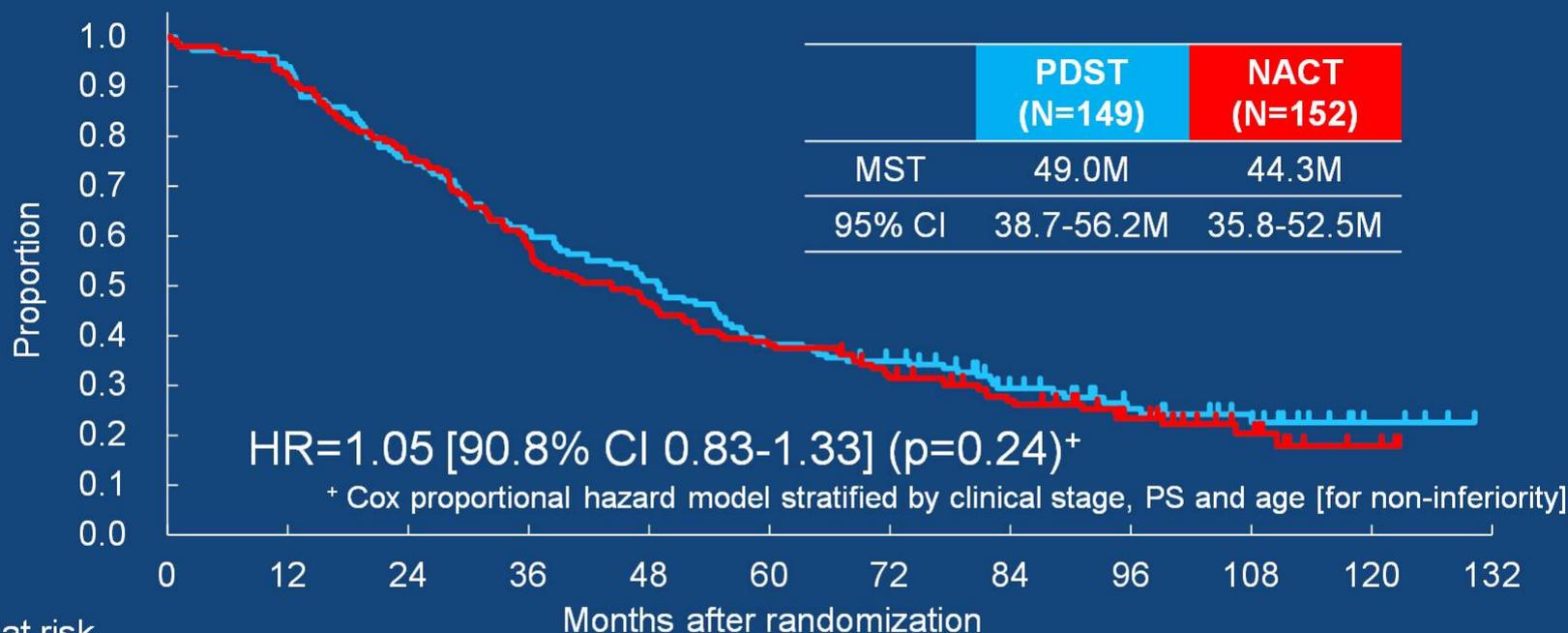
Only ± 66% completed scheduled Tx

Surgical Procedures

	PDST PDS (N = 147)	PDST PDS ± IDS (N = 147)	NACT IDS (N = 130)
Median Operation Time (min)	240	347	302
Complete Surgery (RT=0)	17 (11.6%)	45 (30.6%)	83 (63.8%)
Optimal Surgery (RT=0 or <1cm)	55 (37.4%)	92 (62.6%)	107 (82.3%)
Pelvic Lymphadenectomy	40 (27.2%)	59 (40.1%)	94 (72.3%)
Para-aortic Lymphadenectomy	17 (11.6%)	29 (19.7%)	64 (49.2%)
Abdominal Organ Resection	40 (27.2%)	56 (38.1%)	36 (27.7%)
Distant Metastases Resection	8 (5.4%)	16 (10.9%)	6 (4.6%)

RT: Residual Tumor

Overall Survival (N=301)

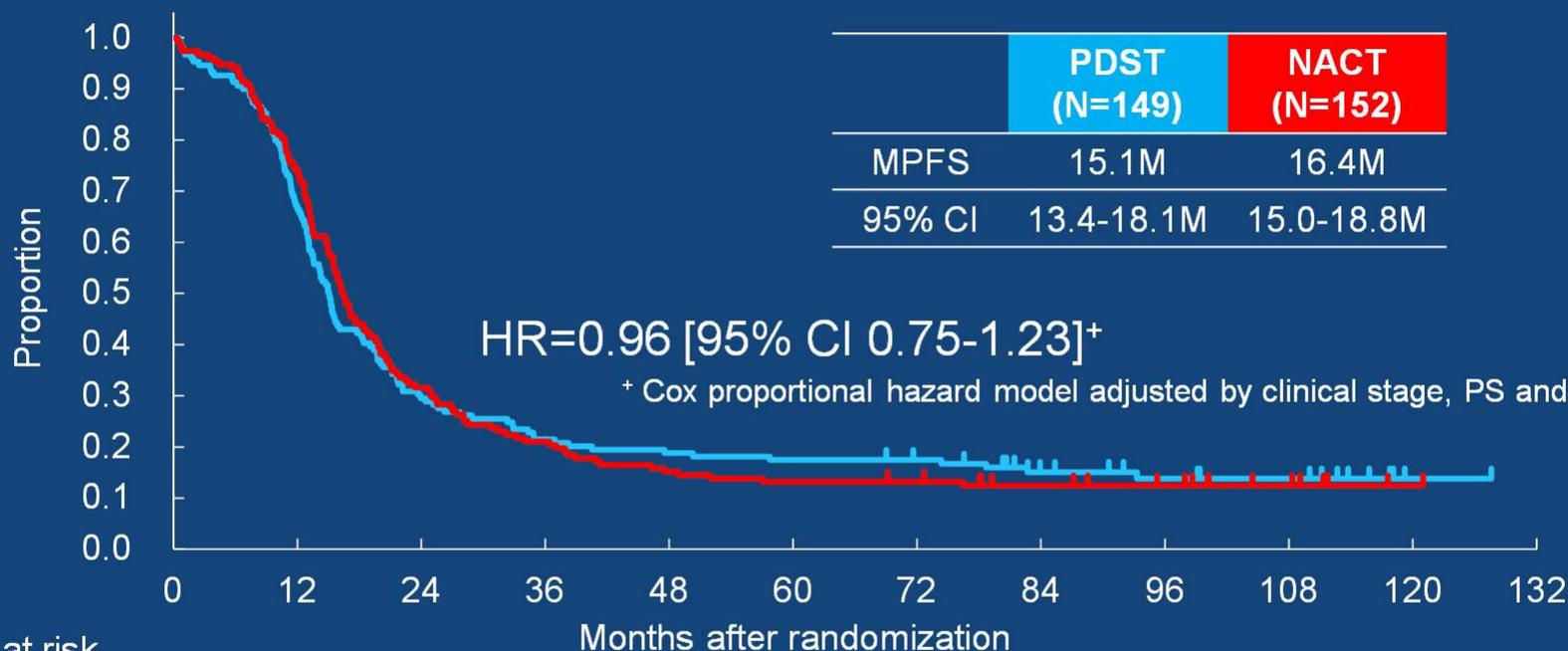


Pts at risk

	0	12	24	36	48	60	72	84	96	108	120	132
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)

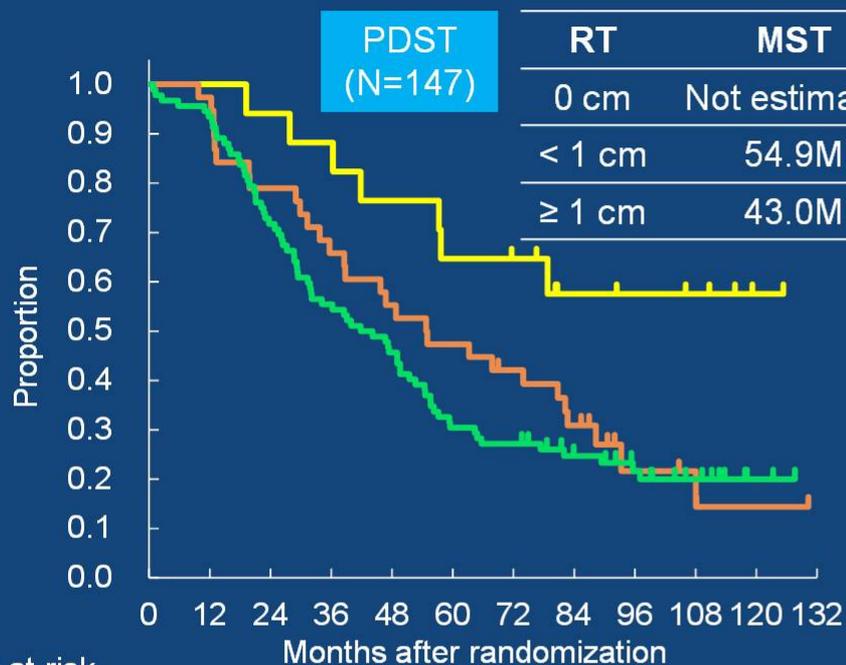
	PDST (N=149)	NACT (N=152)
MPFS	15.1M	16.4M
95% CI	13.4-18.1M	15.0-18.8M



Pts at risk

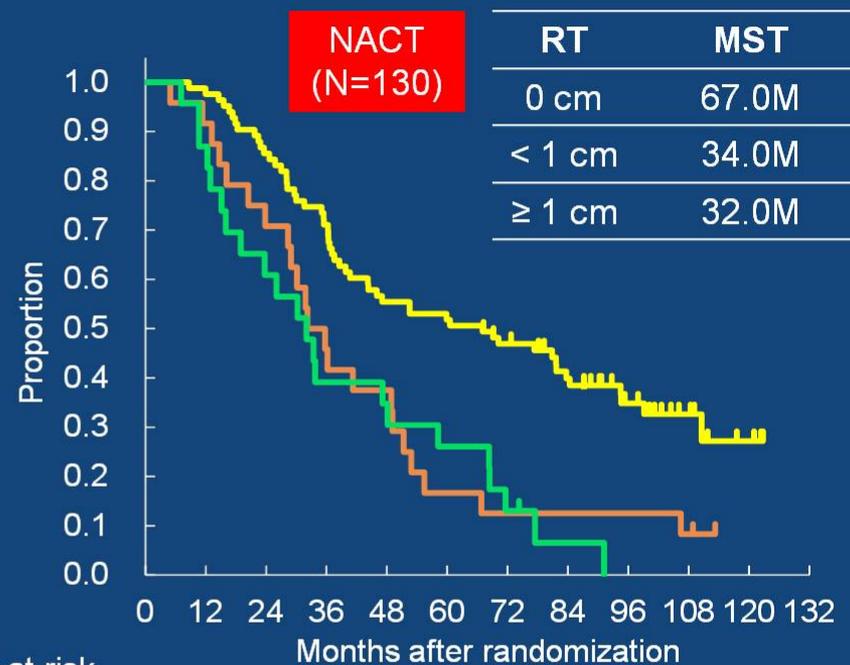
	0	12	24	36	48	60	72	84	96	108	120	132
Arm A	149	99	44	32	28	26	24	15	11	9	1	0
Arm B	152	112	48	32	23	20	19	14	11	6	1	0

OS according to Debulking Results



Pts at risk

	0	12	24	36	48	60	72	84	96	108	120	132
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



Pts at risk

	0	12	24	36	48	60	72	84	96	108	120	132
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

Subset Analysis (Institutional Study Activity)

PDS + NACT
Opt. Resect.
 High \geq 60%
 Low < 60%

Category	Study activity	
	High(N=140)	Low(N=161)
Age	59	61
Stage IV	35%	29%
Alb \leq 2.5 g/dl	9%	16%
PS 2-3	12%	14%
CA125 (U/ml)	1705.5	1603
PDS in PDST	(N=72)	(N=75)
Optimal rate	51%	24%
Operation time (min)	304	175
IDS in NACT	(N=60)	(N=70)
Optimal rate	82%	83%
Operation time (min)	320	284
HR for NACT	1.36(0.92-2.01)	0.86(0.61-1.22)



Comparison of Operative Parameters

Operative parameters	EORTC(2010)		CHORUS(2015)		JCOG		
	PDS in PDST (N=310)	IDS in NACT (N=322)	PDS in PDST (N=251)	IDS in NACT (N=217)	PDS in PDST(N=147)	PDS±IDS	IDS in NACT (N=130)
Operation time(min)	165	180	120	120	240	347	302
Complete Surgery	61(19%)	151(51%)	39(17%)	79(39%)	17(12%)	45(31%)	83(64%)
Optimal Surgery	131(42%)	238(81%)	96(41%)	147(73%)	55(37%)	92(63%)	107(82%)
PLA	58(19%)	77(24%)	7(3%)	2(1%)	40(27%)	59(40%)	94(72%)
PALA	26(8%)	49(15%)	3(1%)	1(<1%)	17(12%)	29(20%)	64(49%)
Bowel Resection	48(16%)	28(9%)	27(10%)	18(7%)	38(26%)	51(35%)	33(25%)
IDS in PDST	57(17%)		NA		49(33%)		
PFS(M) *	12	12	11	12	15		16
OS(M) *	29	30	23	24	49		44

PLA: pelvic lymphadenectomy, PALA: para-aortic lymphadenectomy *among all registered patients

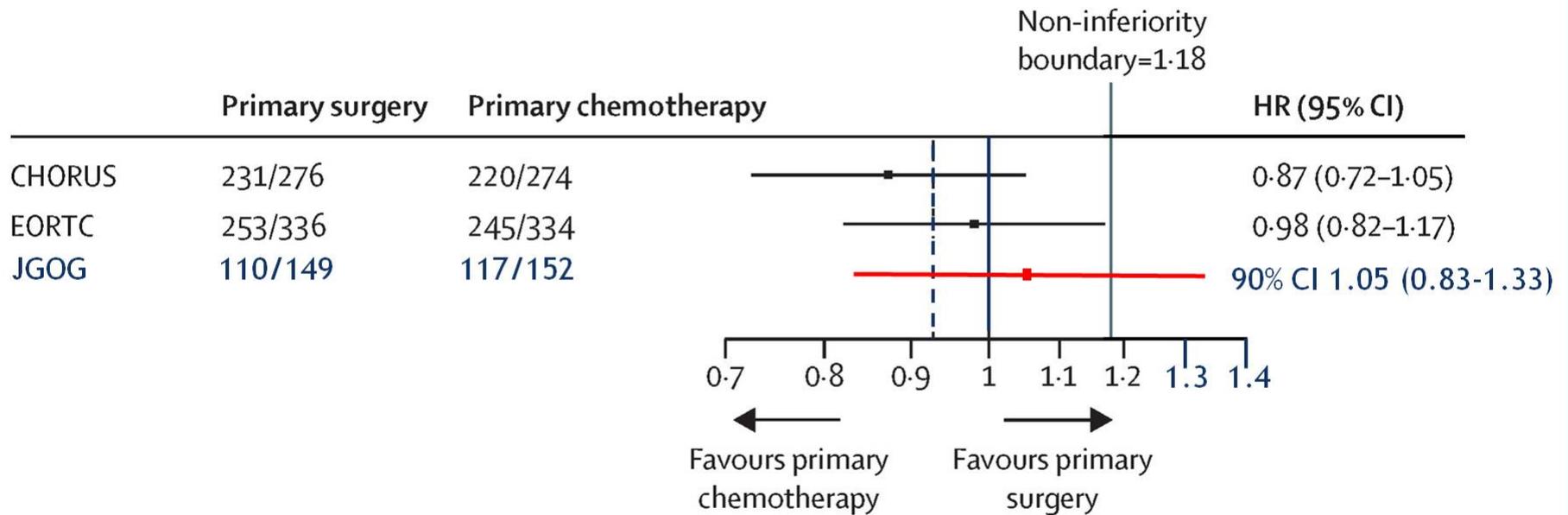
Summary

1. Non-inferiority of NACT compared with PDST was not confirmed in OS.
2. Treatment effect on OS of NACT within major subgroups was assessed.
 - 1) PS 2/3, serum Alb ≤ 2.5 , CA125 > 2000 , and institution with low study activity were advantageous to NACT, and clear/mucinous (chemoresistant) histology was disadvantageous to NACT, though there were no significant differences.
 - 2) Institution with high surgical activity was associated with better outcome of both arms.
 - 3) Advantage of NACT in institutions with low study activity may be not only due to lower optimal debulking rate in PDS but also due to poorer pre-treatment condition (lower serum Alb level).

Conclusions

1. NACT cannot be always a substitute for PDST in first-line treatment of advanced ovarian, tubal, and peritoneal cancer.
2. NACT can be possibly a substitute for PDST in patients with poor general condition and in patients supposed with chemosensitive histology.
3. Further studies may be necessary to demonstrate a role of NACT.

Randomized Trials: PDS vs NACT



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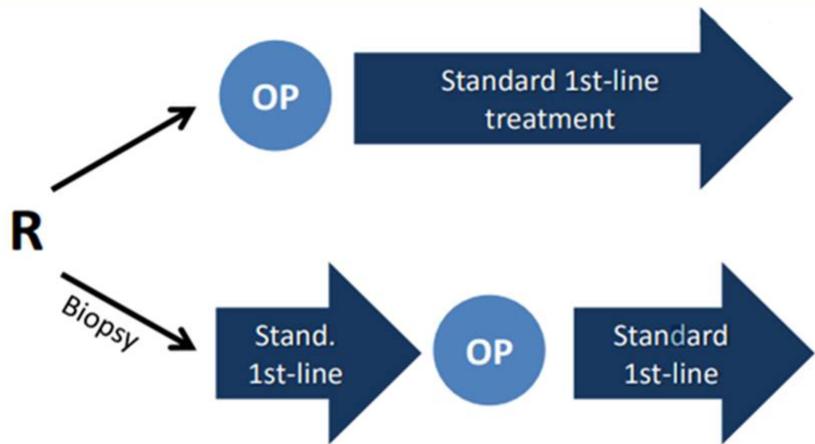
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Kehoe, S et al. Lancet, 386:249-257, 2015
Vergote, I et al. NEJM, 363:943-953, 2010
Onda, T et al. Proc ASCO, Abst 5500, 2018



International TRUST Study

Pt with ovarian-, tube- or peritoneal carcinoma
FIGO Stage IIIB- IV



- Eligibility includes Institutional Surgical Quality Assessments:
≥50% CGR rate for stage III/IV
≥36 PDS cases/year
incl upper abdominal resections
- T/C Bev w/ maintenance
- T/C, Docetaxel/Carbo, Single agent Carbo and study protocols allowed in both arms
- Primary Endpoint: OS
- Secondary Endpoints: PFS, TFT, Complications, QOL



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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



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PRESENTED BY: ROBERT L. COLEMAN, MD

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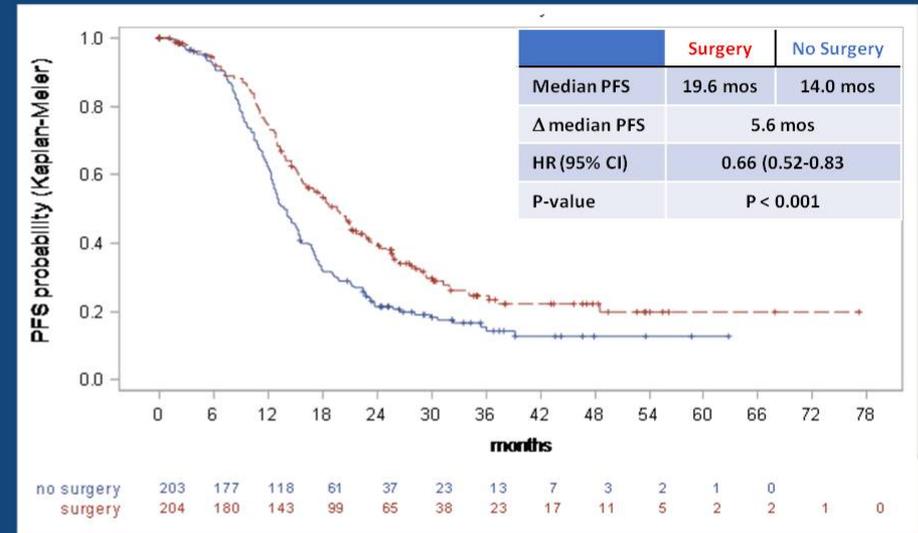
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Background: DESKTOP III

- 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



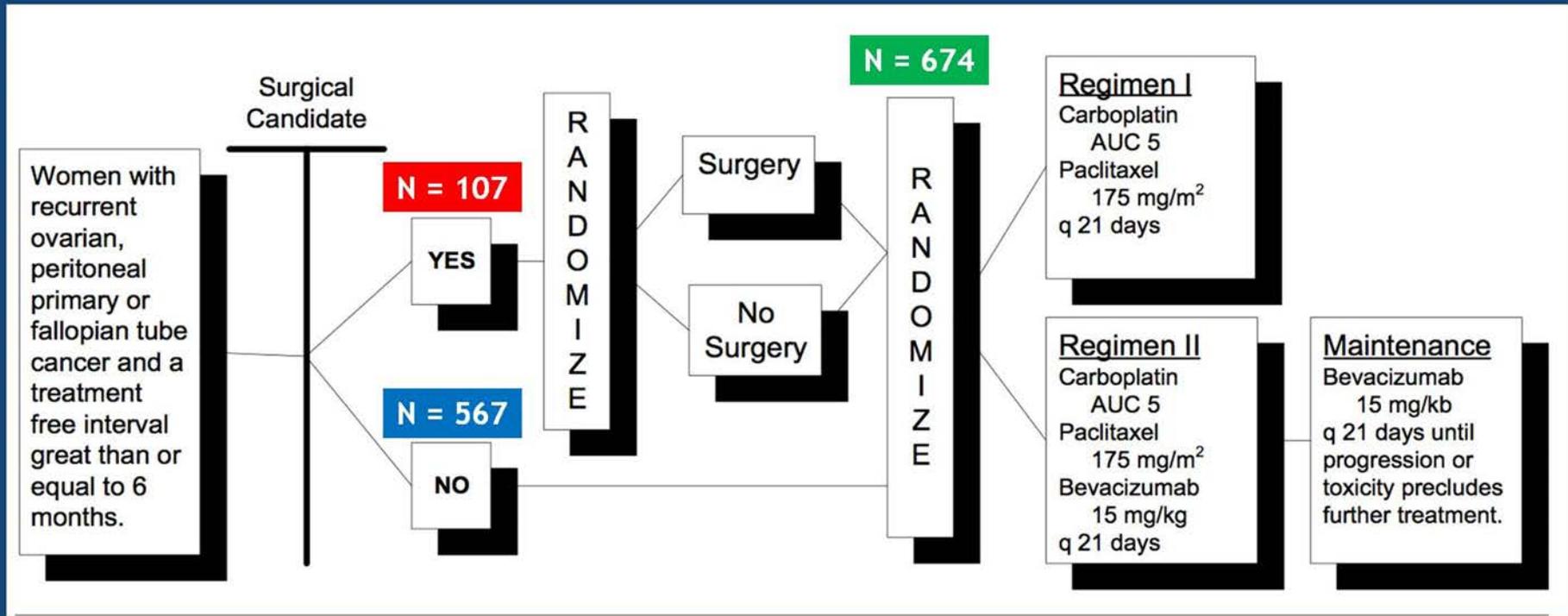
DuBois, Proc ASCO, Abst 5501, 2017

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GOG 213: Schema Objective #1

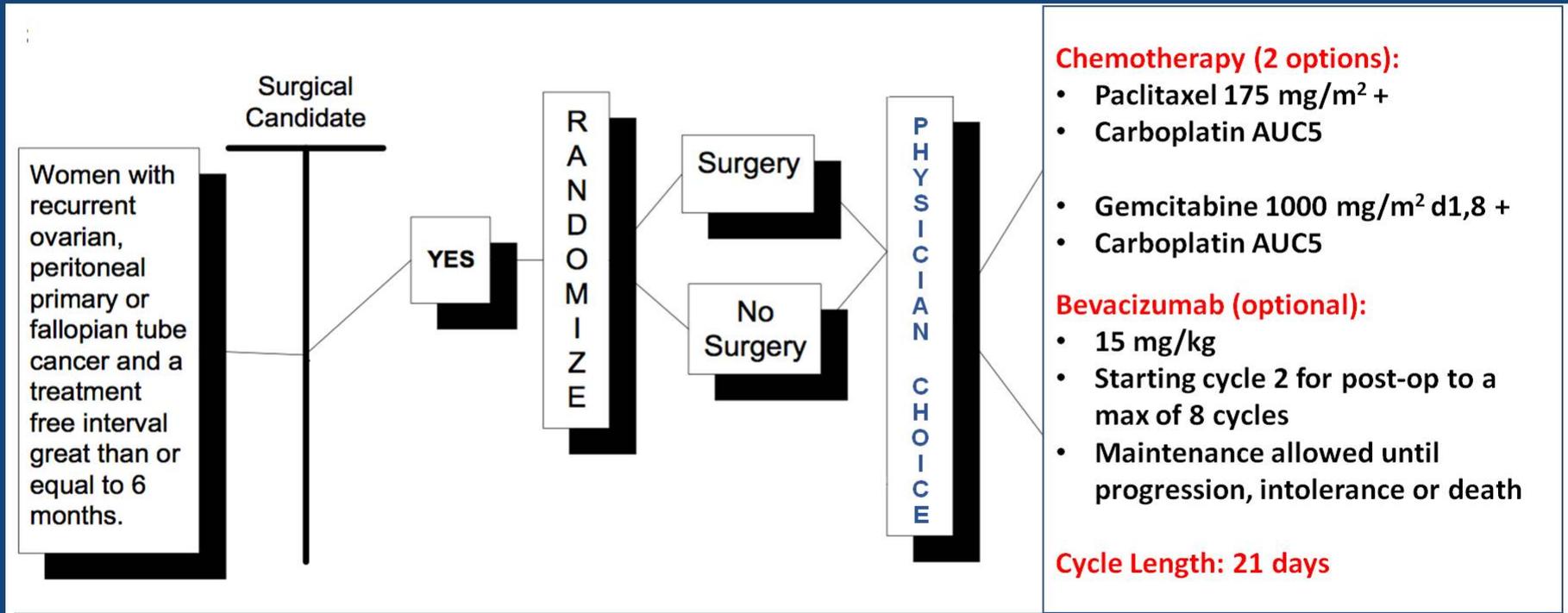


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GOG 213: Schema Modification 8/29/2011



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GOG 213: Primary Objectives

- **Objective #1:** To determine if the addition of **BEVACIZUMAB** to paclitaxel and carboplatin followed by maintenance bevacizumab will INCREASE OVERALL SURVIVAL relative to paclitaxel and carboplatin alone in patients with platinum-sensitive recurrent ovarian cancer
- **Objective #2:** To determine if **SECONDARY CYTOREDUCTION** followed by chemotherapy will INCREASE OVERALL SURVIVAL in patients with platinum-sensitive recurrent ovarian cancer

GOG 213: Eligibility

Ovarian Cancer with a Complete Response front-line therapy

- Clinical CR: negative exam and CA125
- Pathological CR: Reassessment procedure SLL
- Maintenance therapy allowed
- Prior bevacizumab allowed

Platinum-free interval: ≥ 6 months

- If maintenance therapy administered, recurrence must be ≥ 6 months from last treatment

Recurrence:

- “Clinically Evident” (measurable or assessable)
- Equivocal disease needed confirmation by biopsy

Eligibility for Surgery

- No specific eligibility criteria provided
- The goal of secondary cytoreduction is:
 - **COMPLETE REMOVAL OF ALL VISIBLE DISEASE.**
- Protocol Guidance:
 - “Women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction.”
 - Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc.) are poor candidates, if the disease is felt unresectable by preoperative evaluation.”
- Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT).

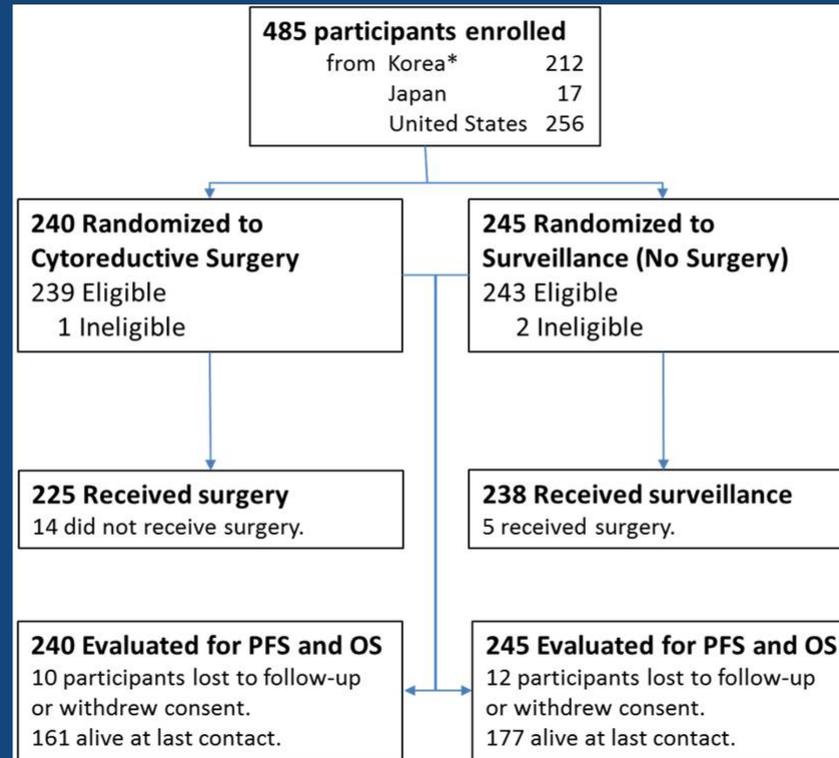
Statistical Design

- 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

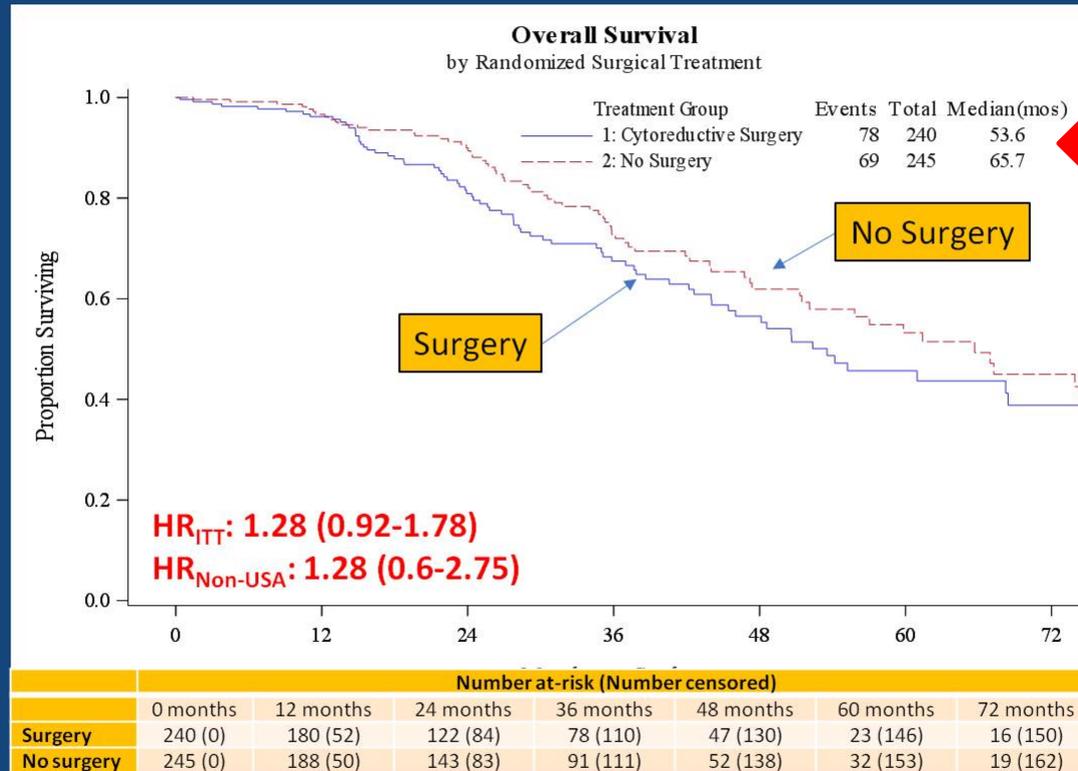
Closed: Jun 9, 2017



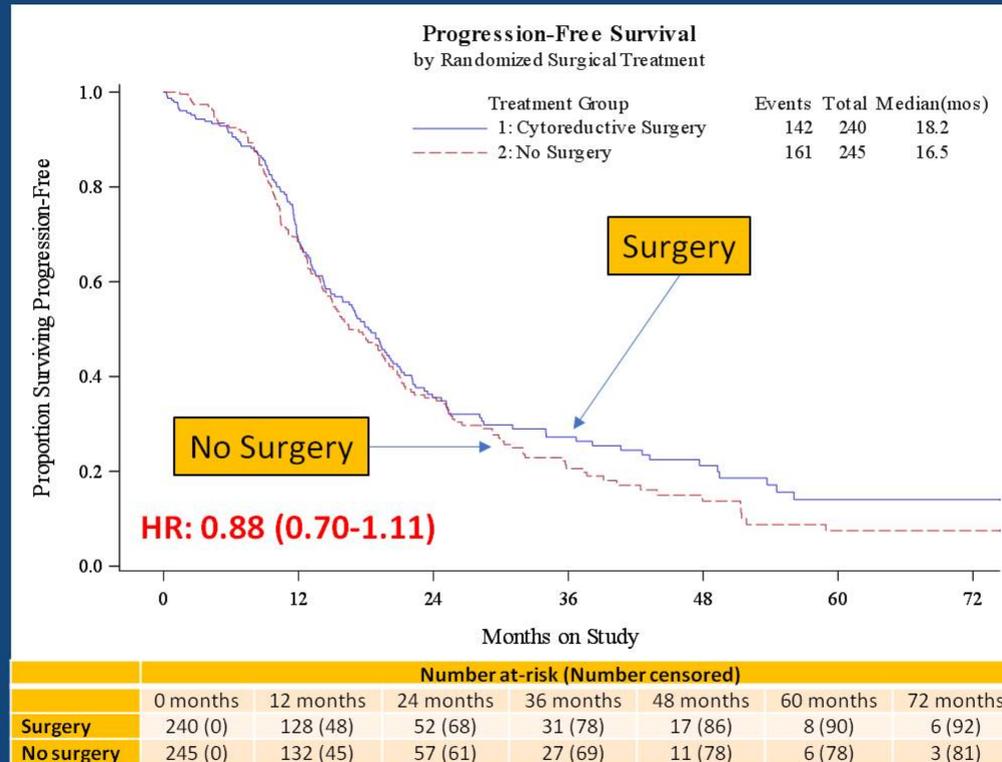
Surgical Findings

- 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

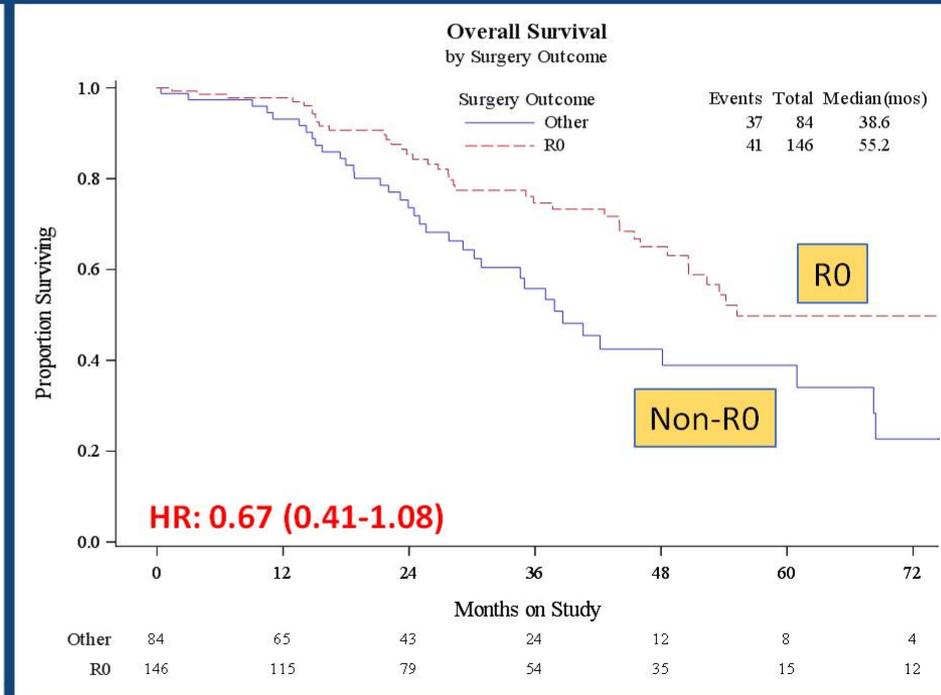
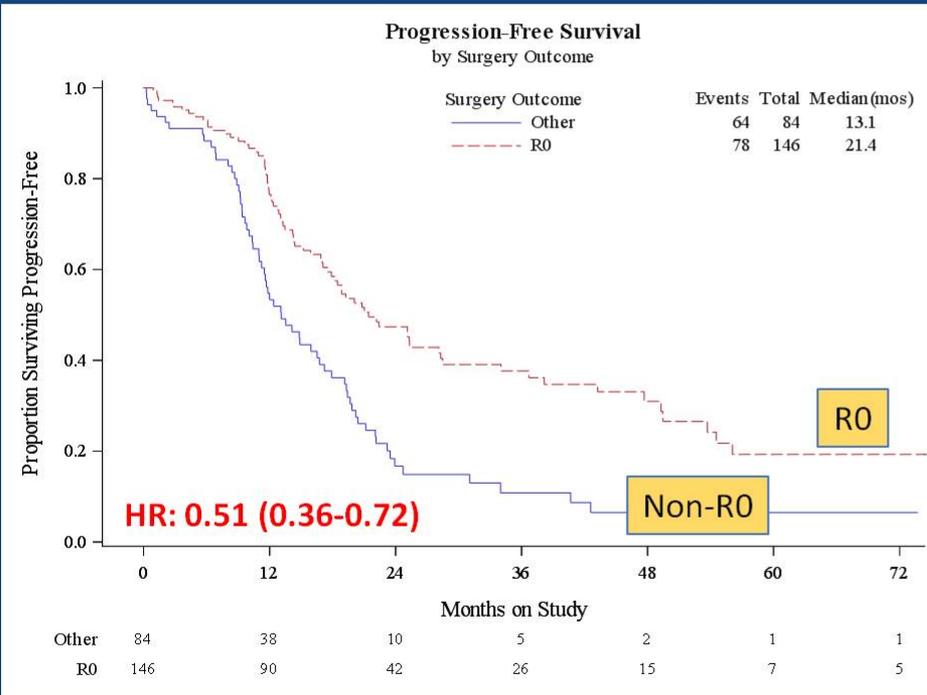


Secondary Endpoint PFS: Surgery vs. Chemo

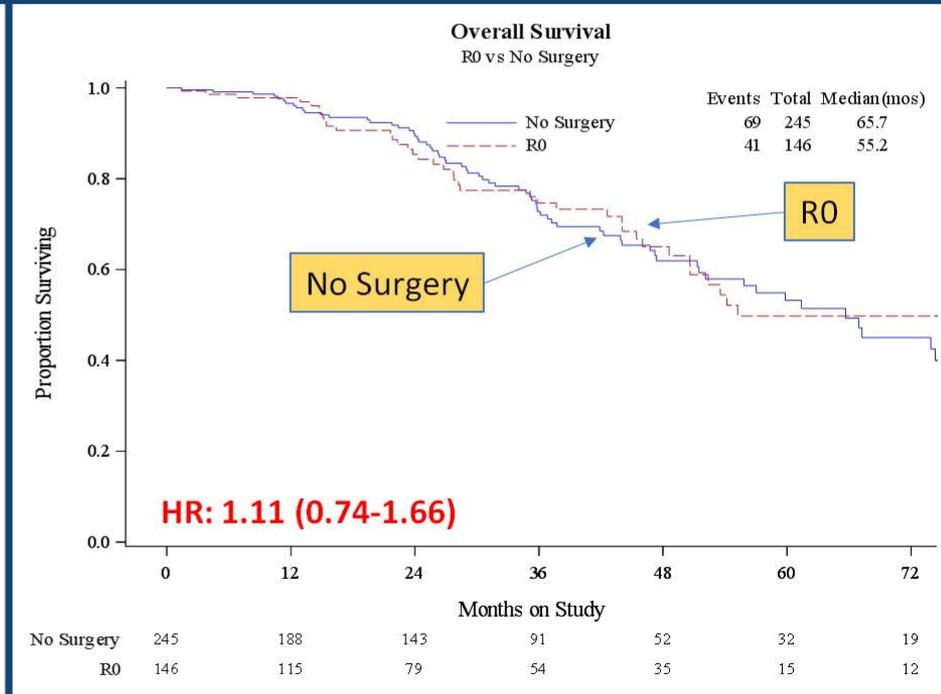
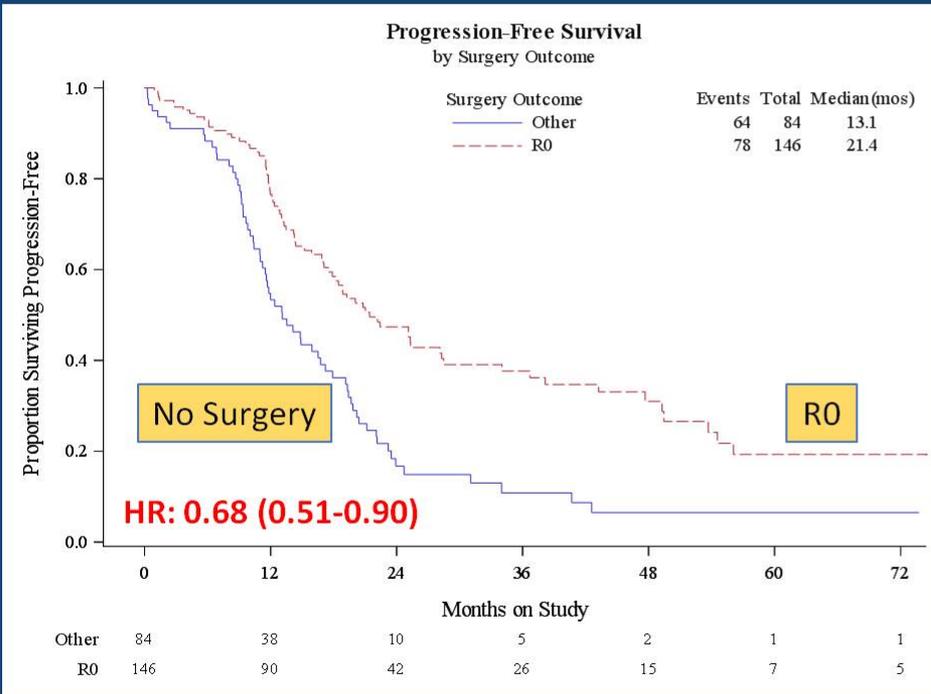


**Desktop III
19.6 vs 14 mths**

Exploratory Endpoint: Surgery Outcome R0 vs. Non-R0



Exploratory Endpoint: Surgical R0 vs. No Surgery



Conclusions

- Secondary cytoreduction was **NOT** associated with an improvement in either OS or PFS compared to no surgery in this population
- Optimal surgical resection (R0) was 68% in the per protocol population and slightly lower than that reported in DESKTOP-III (72.5%, P=0.27)
 - R0 resection statistically improved PFS and OS relative to those with post-operative residual disease
 - However, relative to chemotherapy alone, R0 was not associated with better OS despite extending PFS
- High rate of adjuvant and maintenance bevacizumab use in GOG-0213 (84%)
 - Substantially higher than DESKTOP-III (~20%)

Comments (1)

GOG 213 OS Results

Treatment Group	N	Median OS (mos)
Chemotherapy Randomization (No Surgery)		
Carboplatin + Tax	337	37.3
Carboplatin + Tax / Bev	337	42.2
Surgical Randomization		
Surgery	240	53.6
No Surgery	245	65.7

- High performing ‘No Surgery arm’ in the surgical randomization

- Case Selection: *“All patients must have had a treatment-free interval without clinical evidence of progressive disease of at least 6 months from completion of front-line chemotherapy*

Patients are not considered candidates for surgical cytoreduction if complete cytoreduction in the estimation of the investigator is impossible or a medical infirmity precludes exploration and debulking.”

NORTHWESTERN UNIVERSITY



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SCHOOL OF MEDICINE



ROBERT H. LURIE
COMPREHENSIVE CANCER CENTER
OF NORTHWESTERN UNIVERSITY

Outcomes and costs of open, robotic, and laparoscopic radical hysterectomy for stage IB1 cervical cancer

Daniel J. Margul MD PhD, Junhua Yang MS, Brandon-Luke L. Seagle MD,
Masha Kocherginsky PhD, Shohreh Shahabi MD EMHA

Northwestern University, Division of Gynecologic Oncology

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Objectives

Compare open and minimally invasive radical hysterectomy for stage IB1 cervical cancer with regard to:

- Surgical complications and costs
 - Premier Healthcare Database (Premier)
- Overall survival
 - National Cancer Database (NCDB)

NCDB Cohort (2010-2013)

38,545 diagnosed with cervical cancer

2,257 with FIGO stage IB1 cervical cancer treated with radical hysterectomy

286 other histology
164 prior cancer
49 inadequate information
49 nonstandard treatment
48 improper staging

596 Excluded

1,661
NCDB Cohort

854 (51%)
Open Radical
Hysterectomy

807 (49%)
Minimally Invasive
Radical Hysterectomy

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Premier Cohort: Costs and Complications

	ORH (n = 1277)	RRH (n = 138)	LRH (n = 169)	P value
Length of stay [IQR]	3 [3, 5]	1 [0, 2]	0 [0, 2]	< 0.001
Surgical admission costs	\$11.4K	\$10.8K	\$8.9K	< 0.001
Readmission	2.3%	1.4%	1.8%	0.173
Transfusions	21.3%	3.3%	5.3%	< 0.001
Overall complications	52.7%	24.9%	23.7%	< 0.001

IQR = Interquartile range

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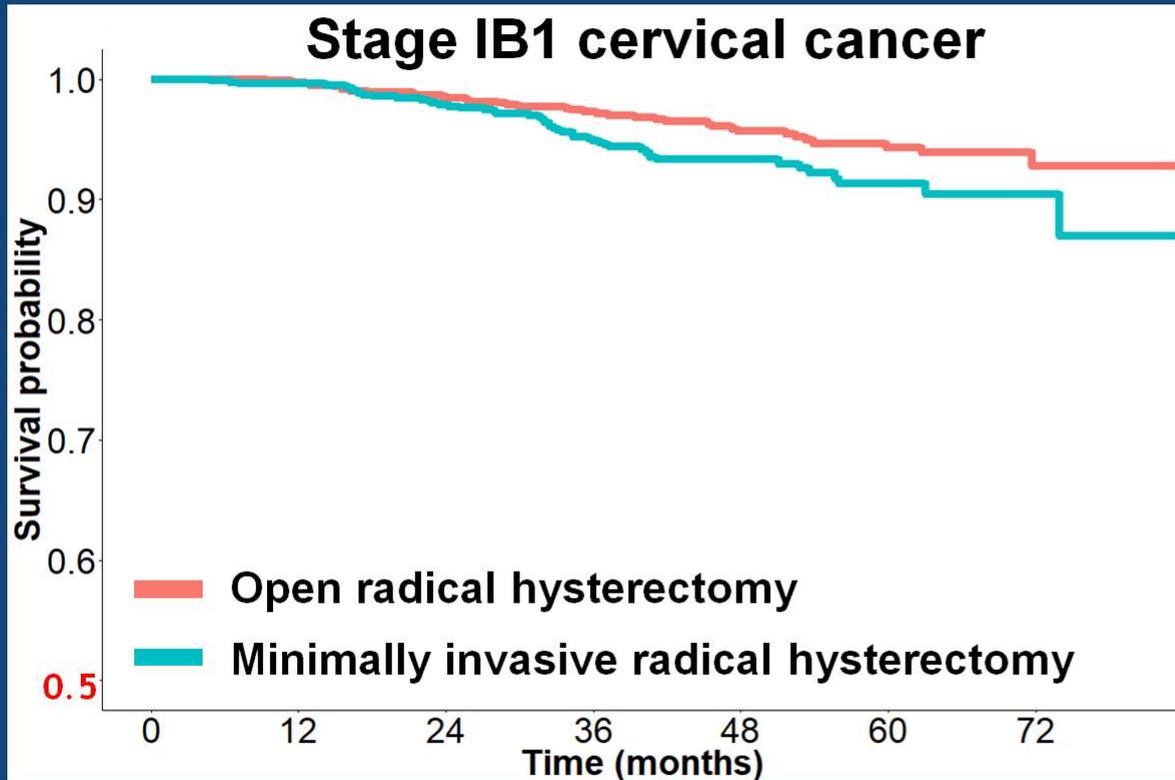
PRESENTED BY: **Daniel Margul MD PhD**

Results: NCDB Cohort Characteristics

	ORH (n = 854)	MIS (n = 807)	P value
Lymph nodes counted [IQR]	18 [12,26]	18 [12,25]	0.764
Positive lymph nodes	6.8%	5.9%	0.443
Positive surgical margins	2.9%	2.9%	0.588
Adjuvant chemoradiation	20.7%	20.4%	0.988
Tumor grade: Grade 3	32.8%	27.0%	0.035
Histology: adenocarcinoma	35.2%	44.1%	< 0.001
Tumor size: 2-4 cm	50.9%	42.1%	0.001

IQR = Interquartile range

Overall Survival by Surgical Approach



Kaplan Meier Method¹

- P=0.021 (log-rank test)

Multivariable Cox model

- HR = 1.92 (95% CI: 1.24-2.96)²
- Similar with imputation and propensity score matching

¹ 87 deaths among 1,661 patients

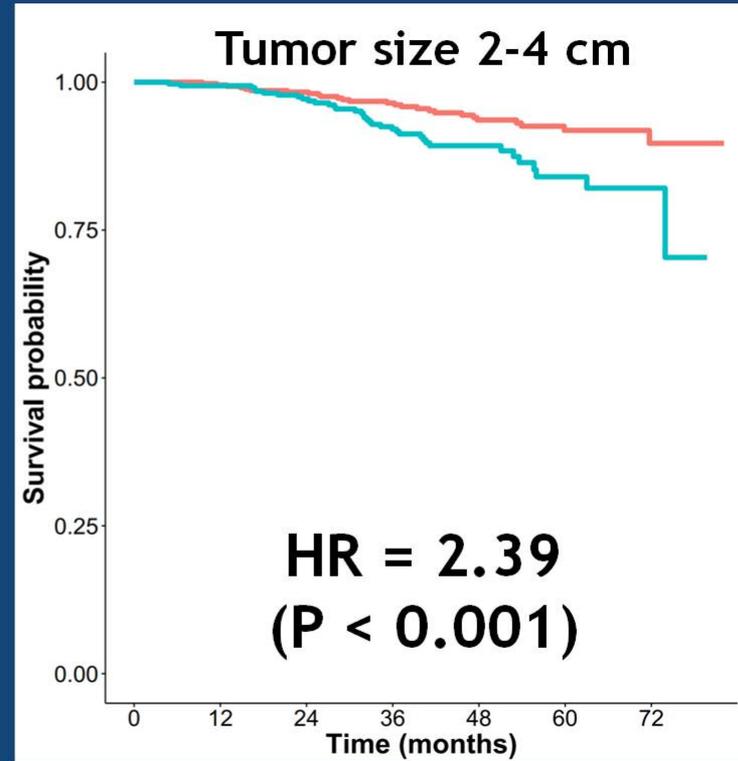
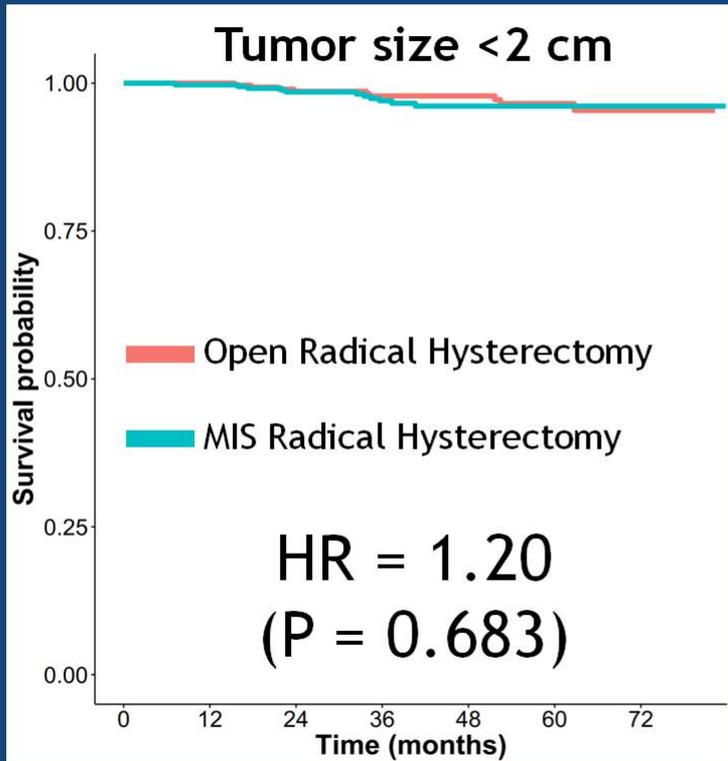
² Covariate adjusted

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Overall Survival by Tumor Size



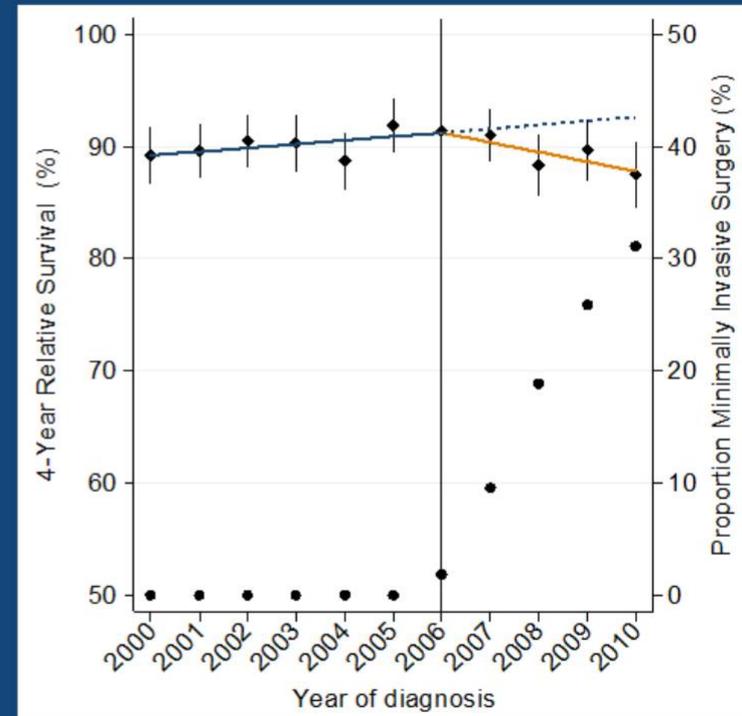
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PRESENTED BY: Daniel Margul MD PhD

Margul DJ et al, Proc ASCO Abst 5502, 2018

MIS Rates and Outcomes in Early Stage Cervical Cancer

- National Cancer Database
- Stage IA2-IB2
- 1166 RH, 1055 MIS
- 79% MIS - Robotic
- MIS rate increasing
- 4Yr Survival decreasing 1%/yr



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PRESENTED BY: Ginger J. Gardner, MD

Chen ML...Rauh-Hain JA, SGO 2018

POST-ASCO

Presented By Ginger Gardner at 2018 ASCO Annual Meeting



Oncologisch Netwerk
Zuidoost-Nederland

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

*Juliet Wolford, MD¹, Jiaru Bai, PhD³, Lindsey Minion, MD¹, Robin Keller, PhD¹,
Ramez Eskander, MD⁴, John Chan, MD⁵, Bradley Monk, MD⁶, Krishnansu Tewari, MD¹*

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³School of Management, Binghamton University, State University of New York, Binghamton, NY

⁴University of California, San Diego, Moores Cancer Center, La Jolla, CA

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⁶Creighton University in Arizona at St. Joseph's Hospital & Medical Center, Phoenix, AZ

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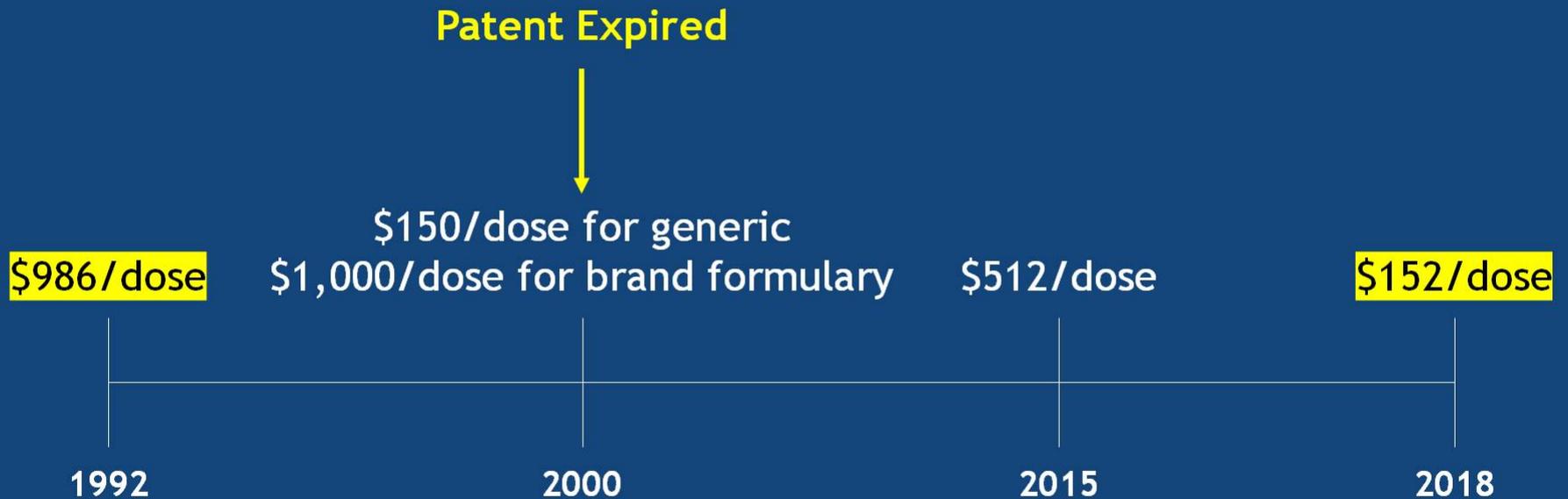
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Cost of Paclitaxel Through Time



Lu Y, et al. *Am J Manag Care.* 2012;18(11 Suppl):S249-56.

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Timeline of Clinical Research + US FDA Approvals Cytotoxic Chemotherapy and Targeted Agents



Note: Pembrolizumab not approved for ovarian cancer.

Adapted from Sun J et al. A systematic analysis of FDA-approved anticancer drugs. *BMC Syst Biol.* 2017;11(Suppl 2):S7.

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OBJECTIVE

- To evaluate and compare the cost-effectiveness of actual and potential maintenance strategies in advanced/recurrent ovarian cancer.

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METHODS : Registration Trials

Maintenance Ovarian Cancer Treatments

Niraparib **(NOVA)**



Olaparib **(SOLO-2)**



Rucaparib **(ARIEL-3)**



Bevacizumab **(GOG218, ICON7, OCEANS, GOG213)**



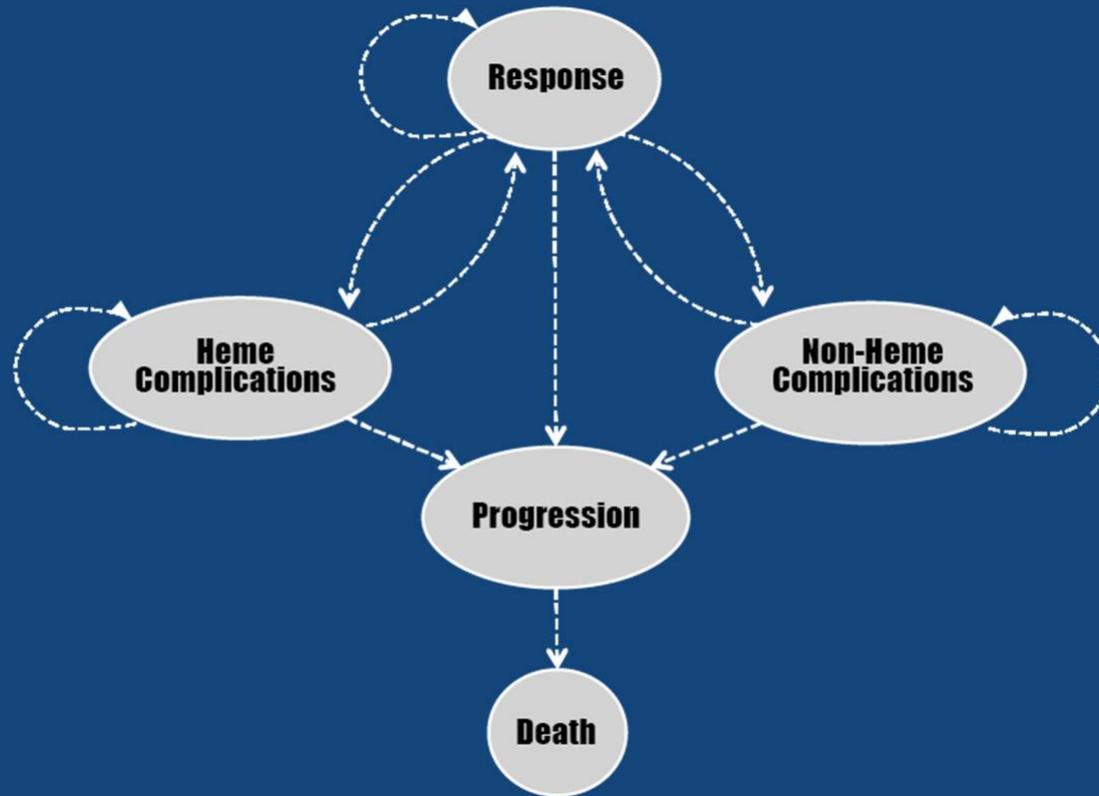
Pembrolizumab **(KEYNOTE-028)**



Paclitaxel **(GOG 212)**



METHODS: Markov Chain



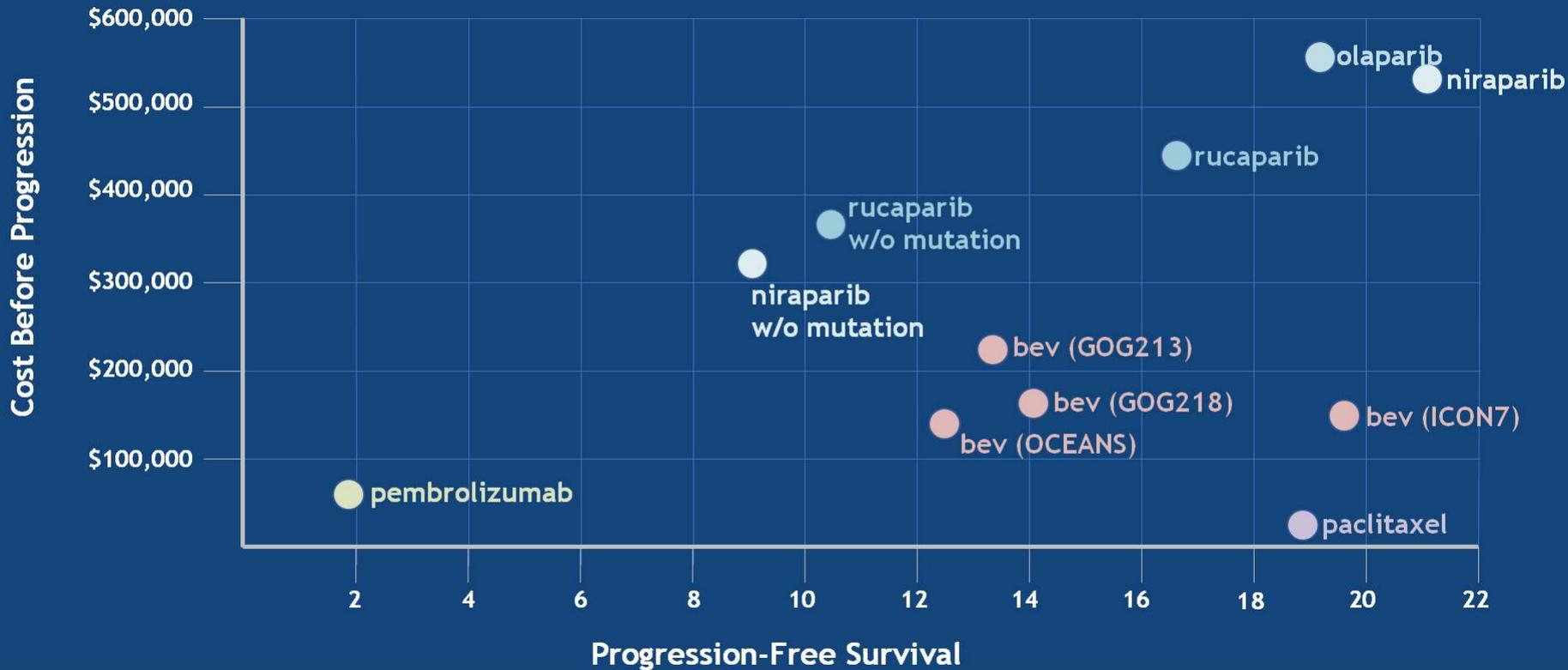
Economic effectiveness assessment

Comprehensive attempt to total up financial cost of each medicine including:

- Drug administration
- Physician costs
- Cost of dealing with toxicities (CTC G3/4 from reg studies)
- Cost of molecular testing

This sort of analysis is crucial as maintenance combinations of two or even 3 drugs are on the horizon

RESULTS: Cost Effectiveness → Cost vs PFS



Calculations are based on PFS which is multifactorial



Calculations are based on PFS which is multifactorial

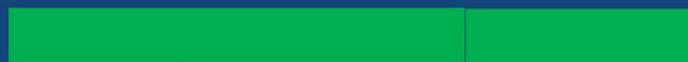
Niraparib BRCA m
(NOVA)



- Platinum-sensitive relapse
- Biologic alone as maintenance

21 months

Bevacizumab
(OCEANS)



- Platinum-sensitive relapse
- Chemotherapy plus biologic (concomitant and maintenance)

12.4 months

Bevacizumab
(ICON7)



- First line
- Chemotherapy plus biologic (concomitant and maintenance)

24.1 months

What is our drug buying us?

Niraparib BRCA m
(NOVA)

5.5 months

15.5 months

21 months

Bevacizumab
(OCEANS)

8.4 months

4.0 months

12.4 months

Bevacizumab
(ICON7)

22.4 months

1.7m

24.1 months

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CONCLUSION

1. High starting costs of PARPi(s) together with daily dosing and longer median PFS associated with germline BRCA mutation carriers make PARPi(s) the least cost-effective of potential maintenance therapies in advanced ovarian carcinoma.
2. Assigning scores to health utility states to account for toxicology does very little to mitigate the high costs associated with these novel targeted therapies.
3. To become cost-neutral with anti-VEGF therapy, PARPi(s) would require significant (i.e., >50%) reduction in cost.
4. Onco-immunology trials in the recurrent disease space need the median PFS benchmark to range between 5 to 8 months.

Medicijnkosten NL

Olaparib € 65.000,= pppj

Bevacizumab € 65.000,= pppj

Overall conclusies Gynoncologia

- PDS met een R0-resectie geeft nog steeds de beste OS data
- NACT + IDS is een redelijk alternatief voor PDS
 - PS 2/3, laag albumine, CA-125 >2000!
 - Ziekenhuizen met een laag % Optimale Debulking?
- De plaats van secundaire debulking bij het (laat) recidief ovariumca is onduidelijk
- Minimaal invasieve chirurgie bij het vroegstadium cervixcarcinoom, niet voor iedereen!
- Kosten van onderhoudstherapie bij het ovariumcarcinoom, aanzienlijk meer dan de medicijnkosten. Weegt de te verwachten winst op tegen de te maken kosten (PFS \neq OS)

