PostASCO 2019

Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: A randomized controlled chemotherapy-free study

ENGOT-OV24/NSGO-AVANOVA2

Mansoor R Mirza[1], E Avall-Lundqvist[2], MJ Birrer[3], R dePont Christensen[4], G-B Nyvang[5], S Malander[6], M Anttila[7], TL Werner[8], B Lund[9], G Lindahl[2], S Hietanen[10], U Peen[11], M Dimoula[12], H Roed[1], A Ør Knudsen[5], L Boufercha[4], S Staff[13], A Krog Vistisen[9], L Bjørge[14], JU Maenpaa[13]

[1]Nordic Society of Gynecological Oncology (NSGO) & Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [2]NSGO & Linköping University Hospital, Linköping, Sweden; [3]The University of Alabama at Birmingham, Birmingham, AL, USA; [4]NSGO Clinical Trials Unit & University of Southern Denmark, Odense, Denmark; [5]NSGO & Odense University Hospital, Odense, Denmark; [6]NSGO & Lund University Hospital, Lund, Sweden; [7]NSGO & Kuopio University Hospital, Kuopio, Finland; [8]University of Utah, Salt Lake City, UT, USA; [9]NSGO & Aalborg University Hospital, Aalborg, Denmark; [10]NSGO & Turku University Hospital, Turku, Finland; [11]NSGO & University Hospital of Herlev, Rungsted, Denmark; [12]NSGO & Sahlgrenska University Hospital, Göteborg, Sweden; [13]NSGO & Tampere University Hospital, Tampere, Finland; [14]NSGO & Haukeland University Hospital, Bergen, Norway

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19
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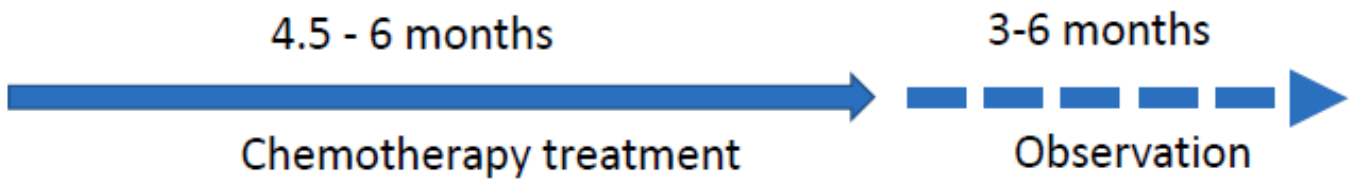
PRESENTED BY: Mansoor Raza Mirza

Presented By Mansoor Mirza at 2019 ASCO Annual Meeting

Current treatment: Platinum combinations for recurrent ovarian cancer

Trial	Regimen	Med PFS (mo)
ICON 4	Carboplatin/Paclitaxel	12.0
CALYPSO	Carboplatin /Paclitaxel	9.4
CALYPSO	Carboplatin/ PLD	11.3
OVAR 2.5	Carboplatin/Gemcitabine	8.6
OCEANS (control)	Carboplatin/Gemcitabine	8.4



- Gaps between successive lines of treatment become shorter

Current treatment: Improving Progression-Free survival by the addition of bevacizumab to platinum-based therapy in recurrent ovarian cancer

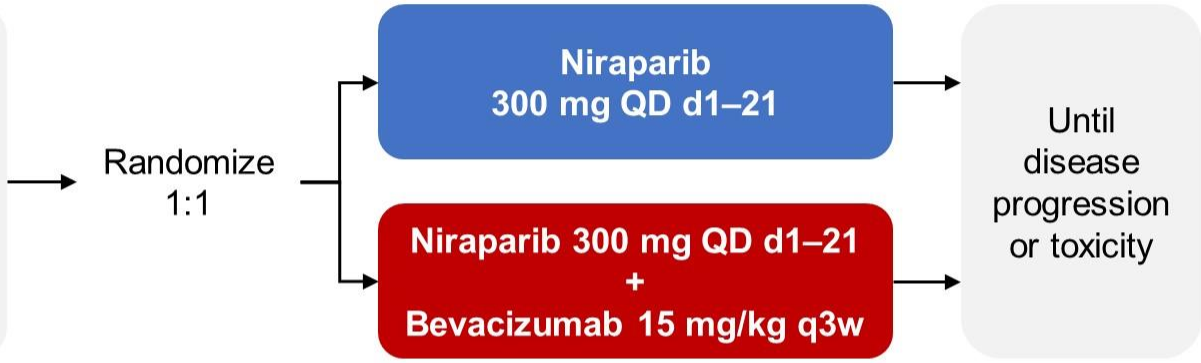
Median Time on treatment

Trial	Regimen	Med PFS (mo)	Med PFS Control (mo)
OCEANS	Carboplatin/Gemcitabine/Bevacizumab	12.4	8.4
GOG 213	Carboplatin/Paclitaxel/ Bevacizumab	13.8	10.4
AGO-OVAR 2.21 / ENGOT-ov 18	Carboplatin/PLD/Bevacizumab	13.3	__
AGO-OVAR 2.21 / ENGOT-ov 18	Carboplatin/Gemcitabine/ Bevacizumab	11.7	__

Aghajanian et al J Clin Oncol 2012; Coleman et al Lancet Oncol 2017; Pfisterer et al ESMO 2018

ENGOT-OV24 / NSGO-AVANOVA2 trial design

- High-grade serous/endometrioid PSROC
- Any number of previous lines of therapies
- Measurable/evaluable disease
- Prior bevacizumab permitted



Stratification factors

- HRD status (positive vs negative)
- Chemotherapy-free interval (6–12 vs >12 months)

Primary endpoint: Investigator-assessed PFS in the ITT population

ITT = intention-to-treat; NCT02354131

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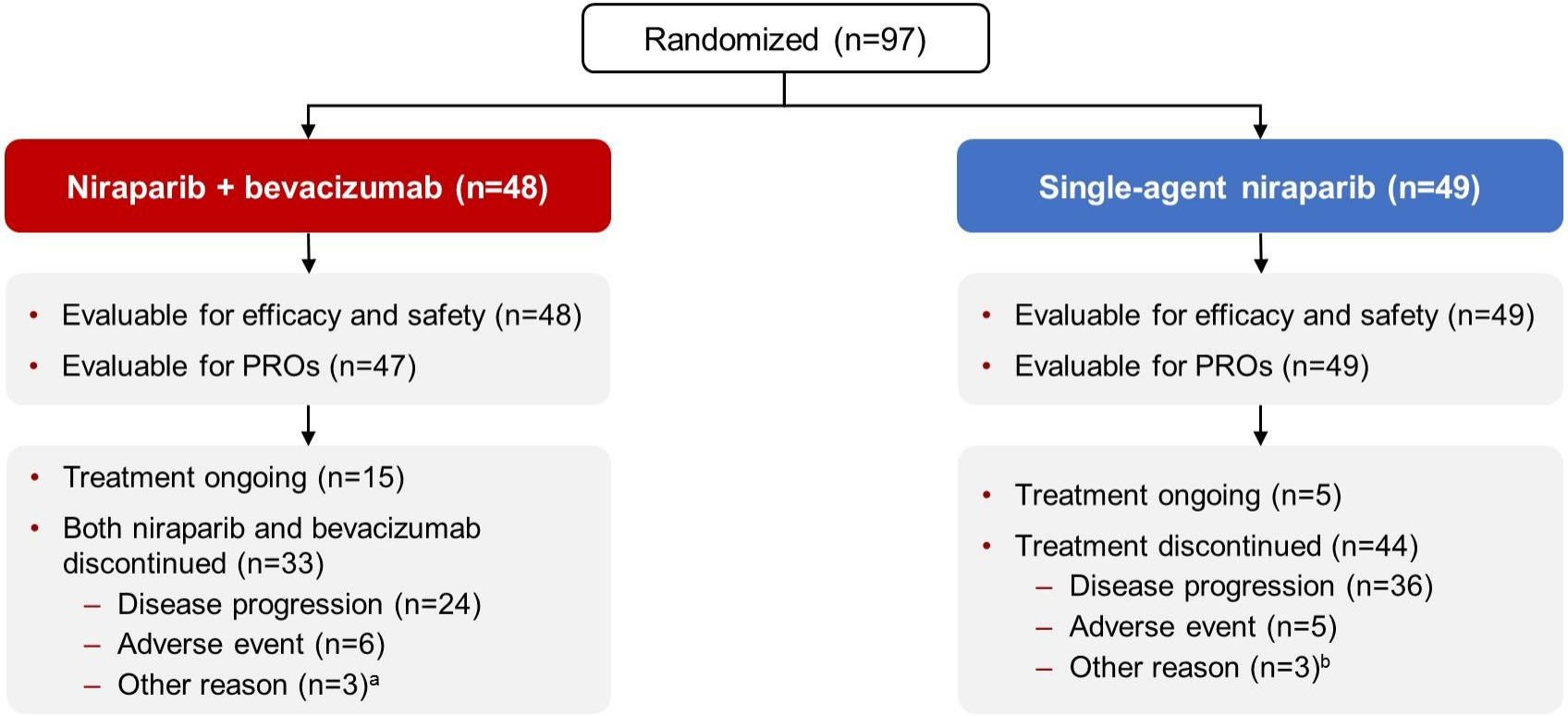
Patient enrollment and disposition



PRO = patient-reported outcome. [a]Performance status deteriorated to 3/4 (n=1), withdrew consent (n=1), other reason (n=1). [b]Investigator decision (n=2), serious compliance issues (n=1).

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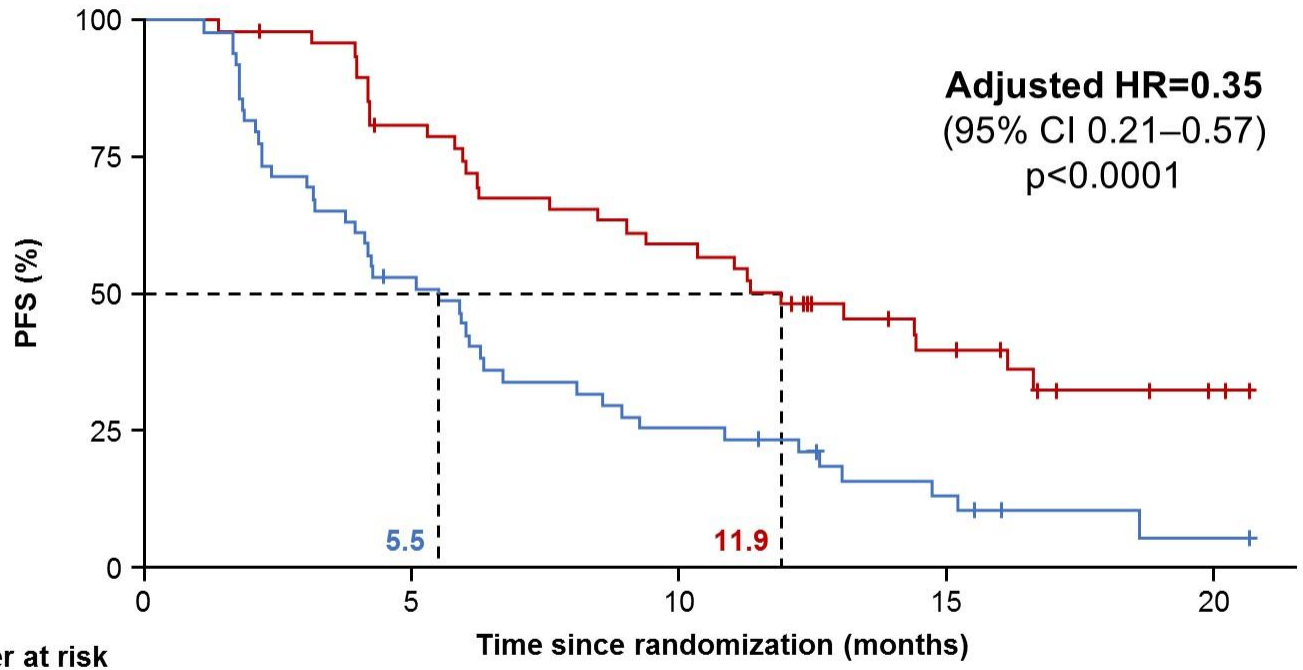
Primary endpoint: PFS in the ITT population



Number at risk					
Niraparib + bevacizumab	48	37	27	14	5
Niraparib	49	25	12	5	1

CI = confidence interval; HR = hazard ratio

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Dose reductions and treatment discontinuations

Number of niraparib dose reductions	Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
None	23 (48%)	21 (43%)
One (300 → 200 mg)	24 (50%)	27 (55%)
Two (300 → 200 → 100 mg)	1 (2%)	1 (2%)

Treatment discontinuations for adverse events	Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
Treatment discontinuation	6 (13%)	5 (10%)

NA = not applicable

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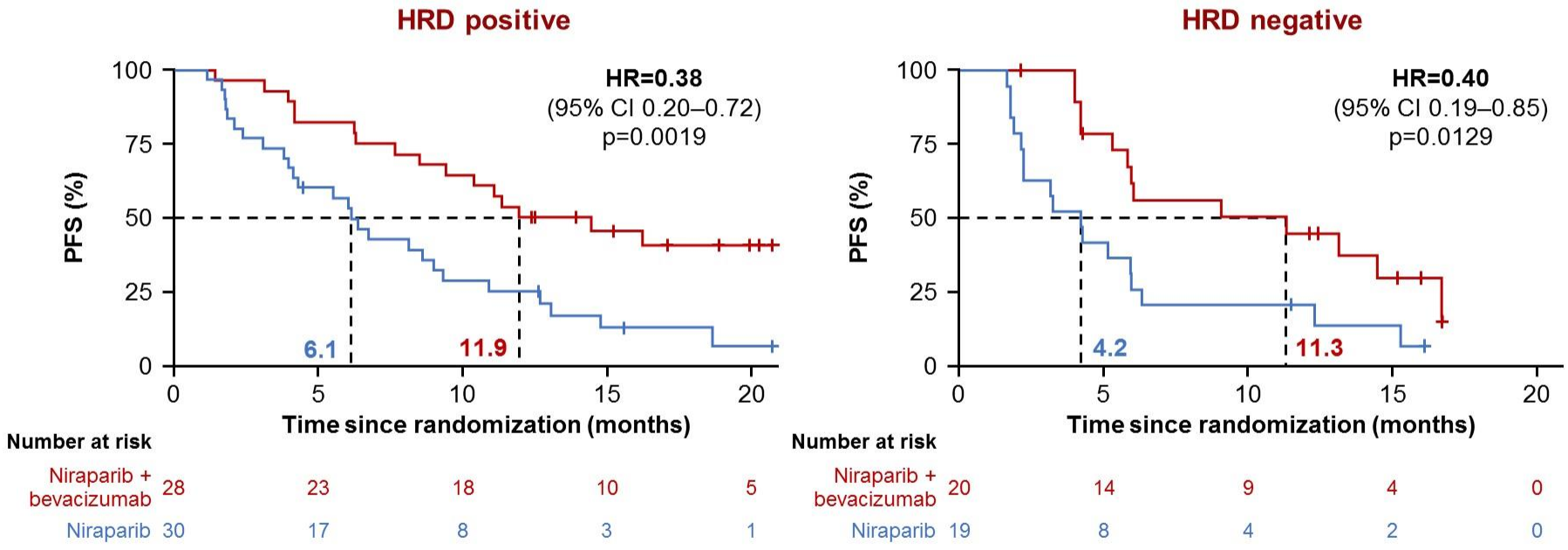
PFS by stratification factors: HRD status



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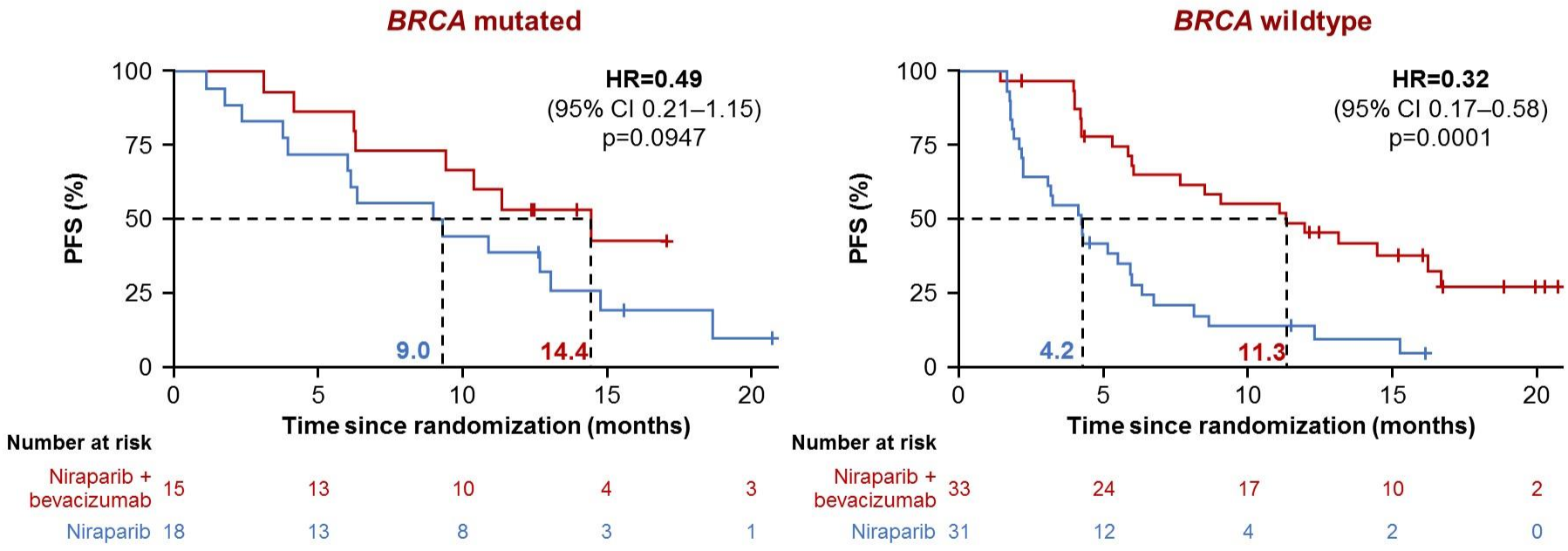
PFS by *BRCA* status



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Conclusions

- NSGO-AVANOVA2 is the first randomized trial to evaluate a chemotherapy-free combination of two established agents approved for use in recurrent ovarian cancer (niraparib and bevacizumab)
- Compared with niraparib alone, the combination of niraparib + bevacizumab as definitive treatment for ovarian cancer significantly improved PFS, regardless of HRD status or chemotherapy-free interval
- Niraparib + bevacizumab combination therapy was well tolerated; most patients remained on treatment until disease progression
- No detrimental effect on quality of life was observed with combination therapy
- A randomized phase 3 trial (NSGO-AVATAR) is planned to compare this regimen vs standard-of-care therapy in PSROC

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GINECO has developed a Geriatric Vulnerability Score (GVS) to discriminate vulnerable from fit older patients (1)

GVS items

- Activity of Daily Living (ADL-Katz) score < 6
- Instrumental Activities of Daily Living (IADL-Lawton) score < 25
- Hospital Anxiety and Depression score (HADS) > 14
- Albuminemia < 35g/L
- Lymphocyte count < 1G/L

GVS = Σ scores

GVS ≥ 3 defines vulnerable older patients (> 70 years old)

(1) Falandry et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial Annals Oncol 2013

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EWOC-1 aim

To determine which is (are) the optimal chemotherapy regimen(s) for older vulnerable patients with ovarian cancer between:

- 3-weekly carboplatin-paclitaxel regimen (standard)
- 3-weekly carboplatin single agent AUC 5-6 (1)
- Weekly carboplatin AUC 2 + paclitaxel 60mg/m² 3wks/4 (MITO5 regimen) (2)

(1) Freyer G. Clinical trials and treatment of the elderly diagnosed with ovarian cancer: Gynecologic Cancer InterGroup. Int J Gynecol Cancer 2011
(2)Pignata S. A phase II study of weekly carboplatin and paclitaxel as first-line treatment of elderly patients with advanced ovarian cancer. A Multicentre Italian Trial in Ovarian cancer (MITO-5) study. Crit Rev Oncol Hematol 2008.

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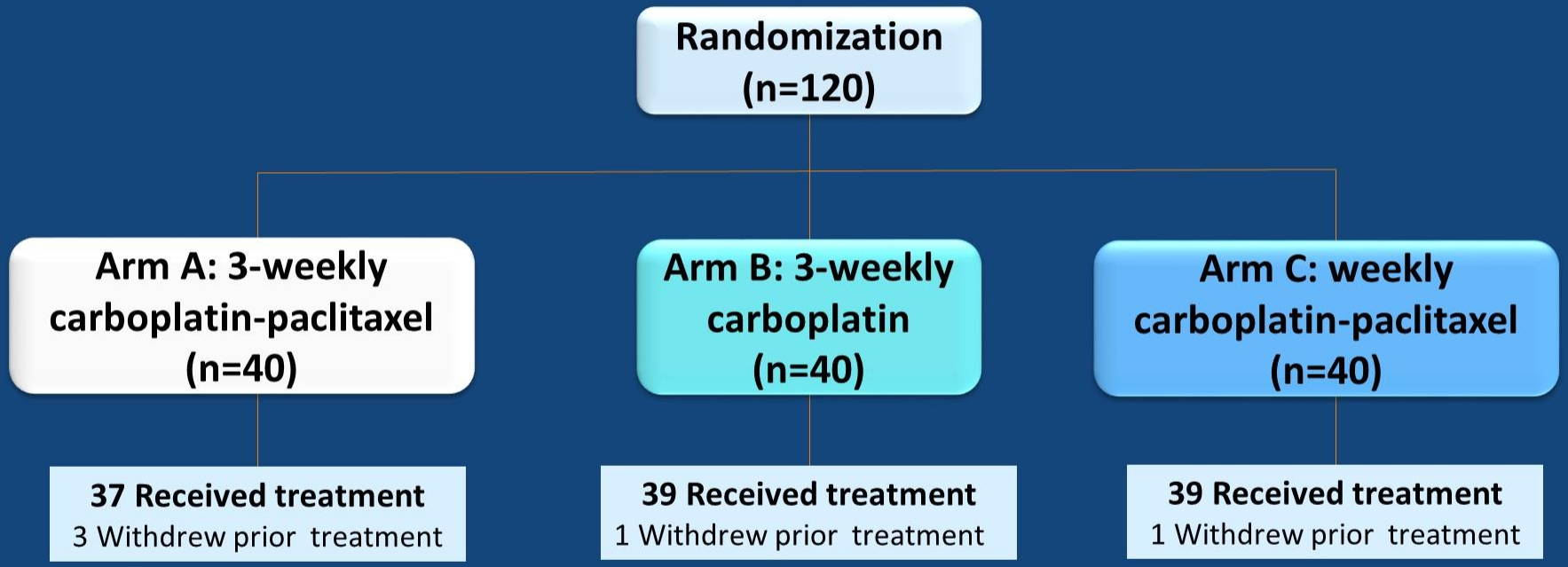
EWOC-1 CONSORT diagram



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EWOC-1 patients' characteristics (1)

Characteristic	Arm A (3wCb-P) N=40	Arm B (3wCb) N=40	Arm C (wCb-P) N=40
Median age, years (range)	79 (71 - 90)	82 (70 - 94)	80 (70 - 90)
GVS global, N (%) **3** **4** **5**	 24 (60) 14 (35) 2 (5)	 19 (48) 14 (35) 7 (17)	 21 (53) 15 (37) 4(10)
GVS per item, N (%)			
Albuminemia < 35 G/L	32 (80)	33 (82)	34 (85)
ADL score < 6	33 (82)	34 (85)	36 (90)
IADL score < 25	36 (90)	37 (92)	37 (92)
HADS > 14	23 (57)	28 (70)	23 (57)
Lymphocyte count < 1.0 10^9/L	14 (35)	16 (40)	13 (32)
Primary tumour location, N (%)			
Ovary	35 (87)	33 (82)	31 (78)
Fallopian tubes	0 (0)	1 (3)	0 (0)
Primary peritoneal	4 (10)	4 (10)	6 (15)
Unknown	1 (3)	2 (5)	3 (7)

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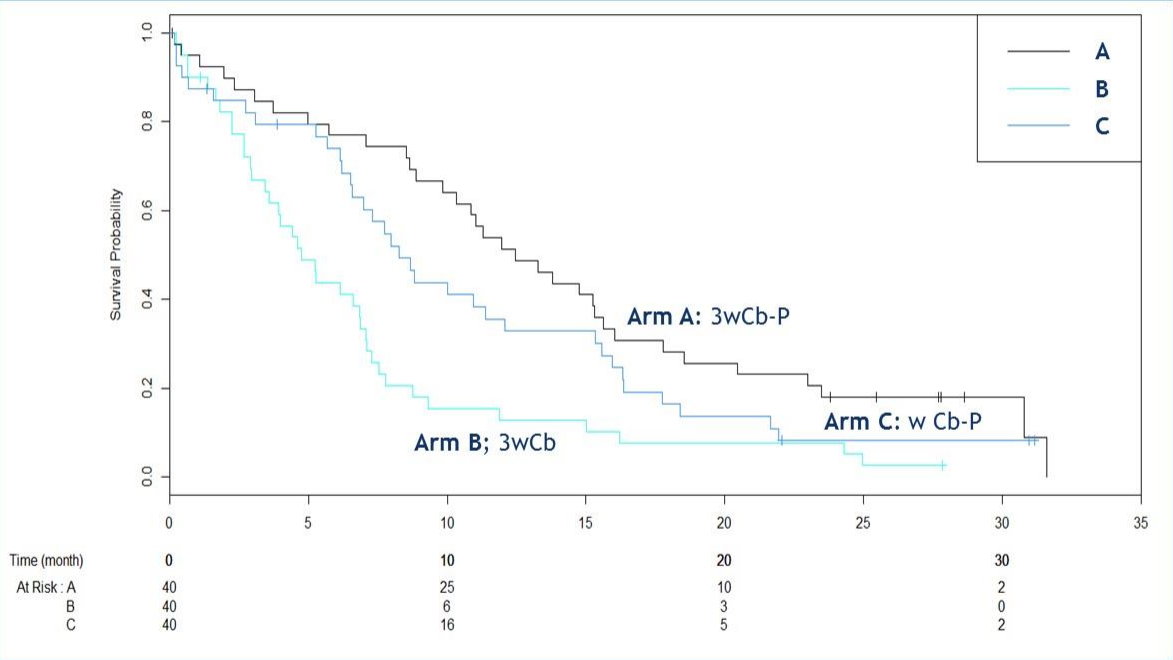
EWOC-1 Progression-free survival



	Arm A	Arm B	Arm C
Events, N (%)	34 (85)	38 (95)	34 (85)
Median, mos (95% CI)	**12.5** (10.3 - 15.3)	**4.8** (3.6-15.3)	**8.3** (6.6-15.3)
HR (95% CI)	1 (REF)	**2.51** **(1.56,4.04)**	1.41 (0.87,2.28)
P Wald test	-	**< 0.001**	0.162
P Log-Rank	< 0.001		

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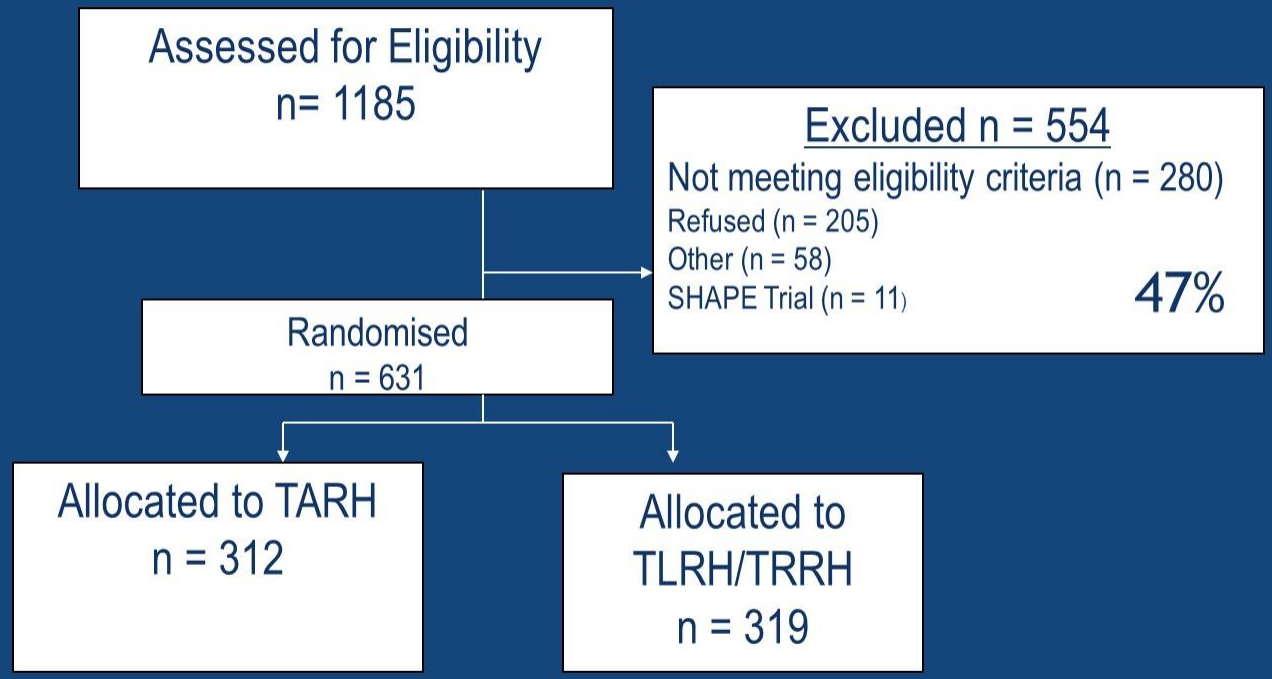
CONSORT Diagram LACC Trial



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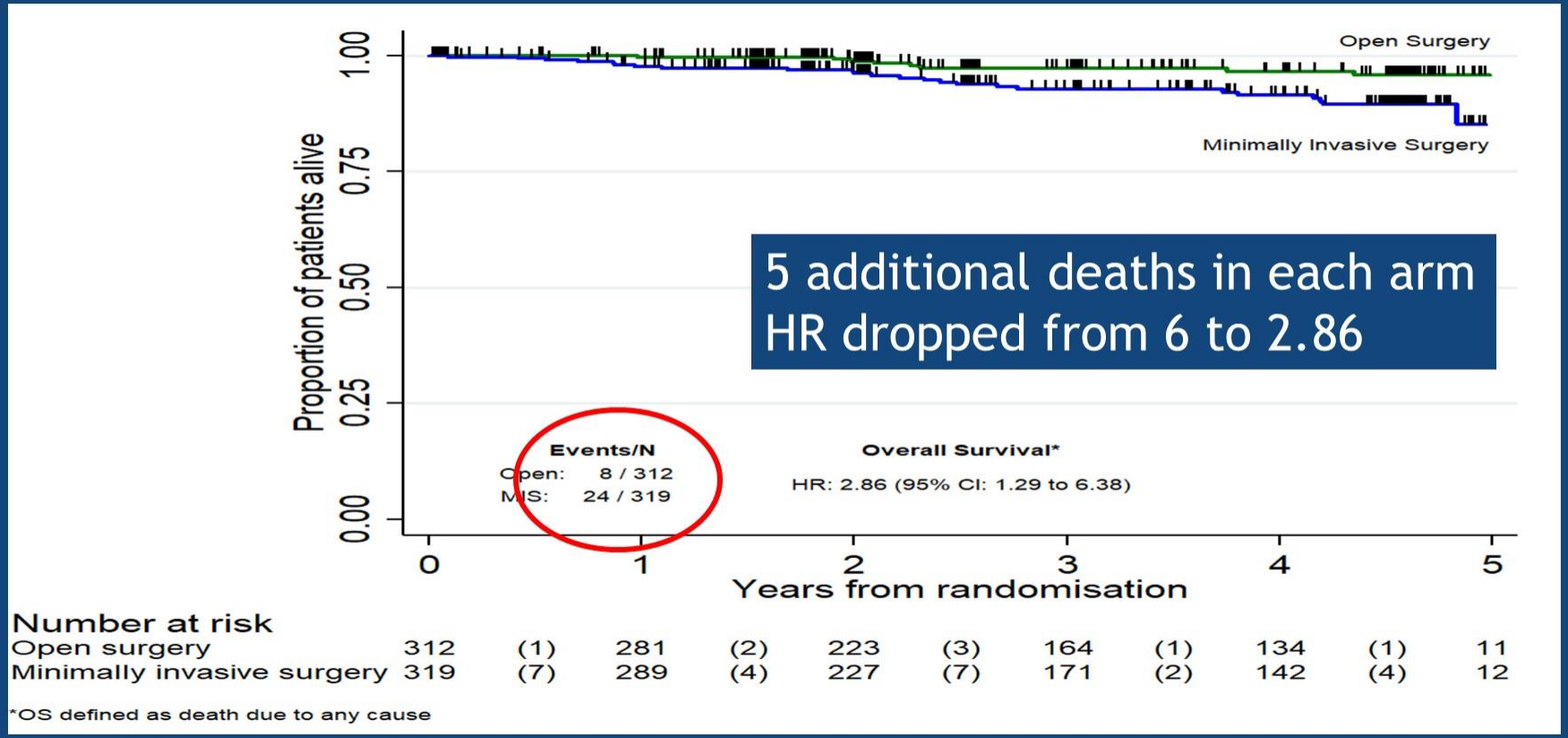
LACC Trial Update 2019



*OS defined as death due to any cause

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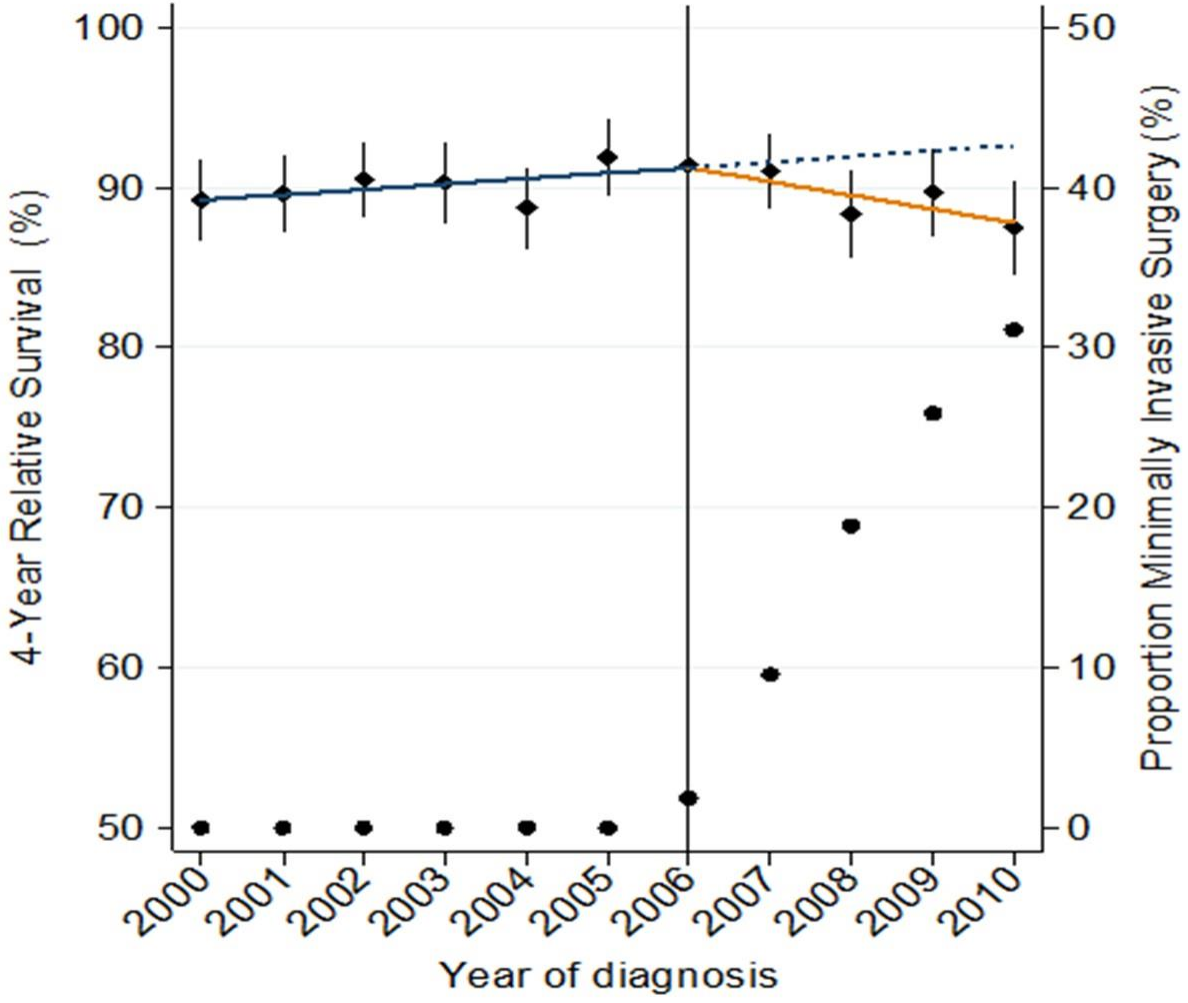
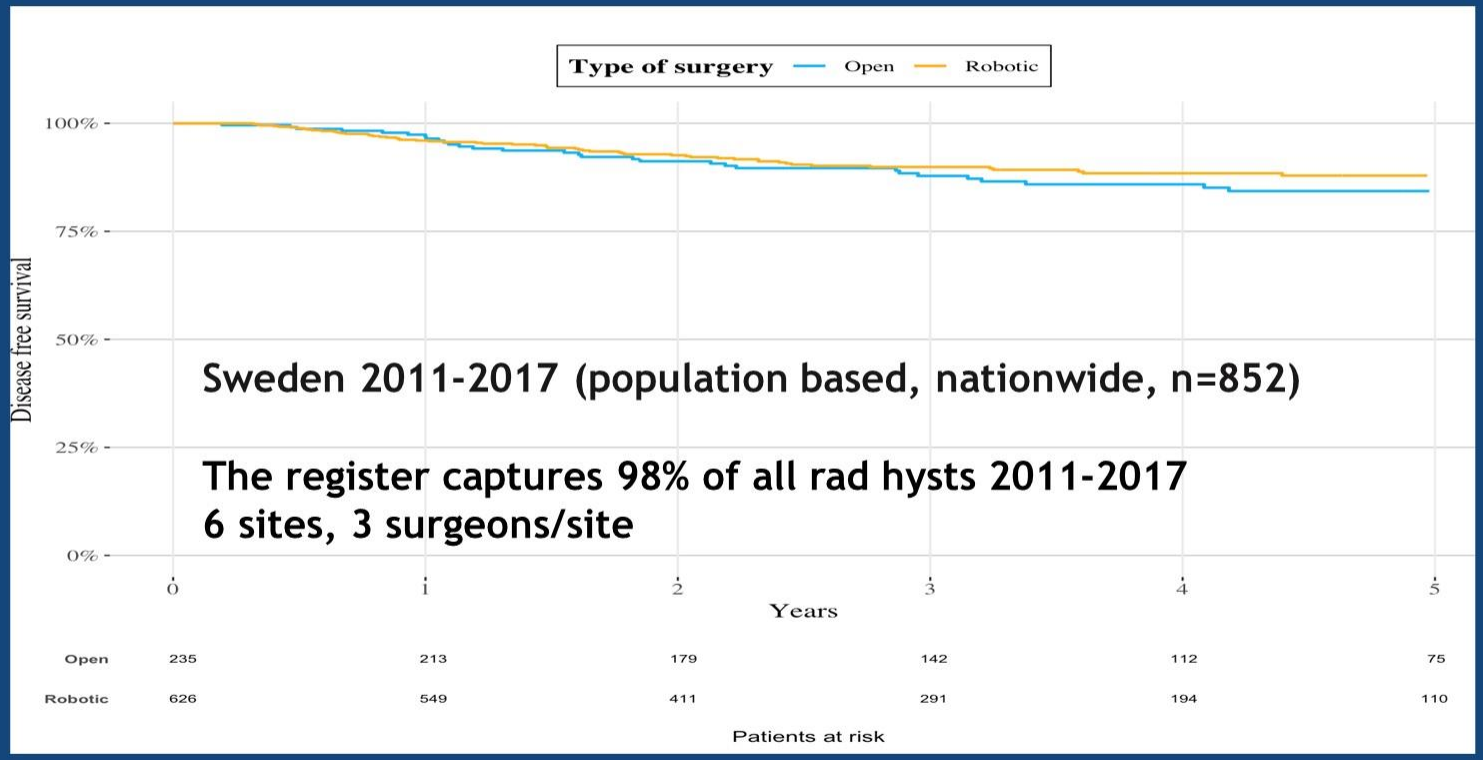
Time Interrupted Series (SEER Data)

Adoption of MIS was associated with a significant change of temporal trend, with **4-year survival declining by 1.0%** (95%CI 0.3-1.6 per year annually after 2006)



Swedish National Registry: DFS (OS = 92%)



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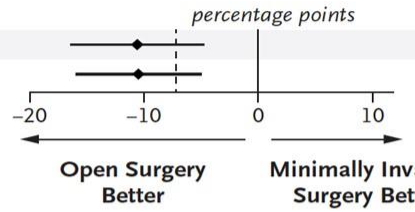
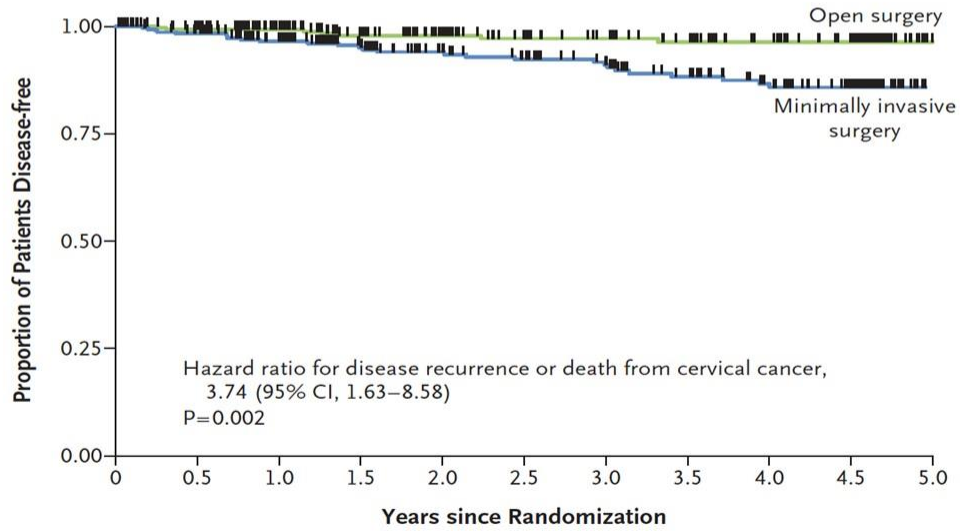
A

Population	Disease-free Survival Rate at 4.5 Yr (95% CI)		Difference (95% CI)	P Value for Noninferiority
	Minimally Invasive Surgery	Open Surgery		
	percent		*percentage points*	
Intention-to-treat population	86.0 (79.7–90.4)	96.5 (92.7–98.4)		0.87
Per-protocol population	87.1 (81.0–91.3)	97.6 (94.1–99.0)		0.88



B



No. at Risk

Open surgery	312	280	236	187	163	144	134	123	104	90	7
Minimally invasive surgery	319	292	244	192	167	155	142	121	102	80	5