2025 ASCO ANNUAL MEETING

AGO STUDY GROUP

TRUST: Trial of Radical Upfront Surgical Therapy in Advanced Ovarian Cancer
(ENGOT ov33 / AGO-OVAR OP.7)

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TRUST Key Takeaway Points

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Patients with advanced ovarian cancer in TRUST had excellent PFS and OS after maximal effort cytoreductive surgery.
Complete resection rates were high and morbidity and mortality were low.

A statistically significant OS improvement for primary compared to interval cytoreductive surgery was not observed.

TRUST is the first randomized phase III trial to show improved median PFS for primary compared to interval cytoreductive surgery without compromising short- or long-term quality of life.

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TRUST Background

- The aim of surgery in advanced ovarian cancer is to prolong patients' remission and improve overall survival while sustaining quality of life.
- Complete gross tumor resection is associated with favorable outcome.[1,2]
- Primary cytoreductive surgery (PCS) followed by chemotherapy was considered standard over decades.
- An alternative strategy with neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) in selected patients (pts) was subsequently reported by randomized phase III trials.[3-6]
- However, these studies had limitations regarding patient- as well as center-selection and surgical quality metrics.
- **As a result, the optimal timing of surgery in pts with advanced ovarian cancer considered resectable remains controversial.**

[1]du Bois et al. Cancer 2009; [2]Bristow et al. J Clin Oncol 2023; [3]Vergote et al. N Engl J Med 2011; [4]Kehoe et al. Lancet 2016; [5]Fagotti et al. Int J Gynecol Cancer 2020; [6]Onda et al. Eur J Cancer 2020

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TRUST Rationale

TRUST was designed to evaluate the optimal timing of maximal effort cytoreductive surgery in patients with advanced ovarian cancer

- considered resectable
- fit enough to tolerate radical surgery
- treated in gynecologic cancer centers with defined surgical quality assurance criteria.

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TRUST Quality Assurance

- Centers were required to obtain accreditation for the trial including onsite quality assurance review.[1]
- Quality criteria were based on ESGO certification[2] and extended for TRUST including
  - evaluation of cytoreductive surgery in the operating room
  - assessment of surgical proficiency and infrastructure
  - complete resection rates (≥50% in upfront surgery for FIGO IIIB-IVB pts)
  - surgical volume (≥36 cytoreductive surgeries/year).

[1]Reuss et al. Int J Gynecol Cancer 2019, [2]Fotopoulou et al. Int J Gynecol Cancer 2020
ESGO: European Society of Gynecologic Oncology

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TRUST Study Design

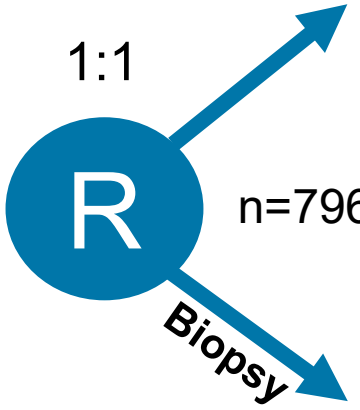
Main Inclusion Criteria

- Epithelial ovarian, fallopian tube or peritoneal cancer
  - FIGO stage IIIB/C, IVA/B
  - Considered resectable
- Fit enough to tolerate radical surgery

Stratification factors

- Center
- Age-ECOG-combination
  ECOG0 and age ≤65y vs.
  ECOG>0 or age >65y

Qualification process for participating centers to ensure surgical quality



Primary Cytoreductive Surgery

Neoadjuvant Chemotherapy + Interval Cytoreductive Surgery

Recommended systemic treatment:

- Carboplatin AUC5, Paclitaxel 175mg/m^2 q3w
- Bevacizumab 15mg/kg q3w as indicated
- PARPi as indicated
- Study participation or any other treatment as long as applicable for both study arms

Primary endpoint

- Overall survival

Key secondary endpoints

- Progression-free survival
- Complete resection rate
- Surgical procedures
- Surgical morbidity
- Quality of life

Predefined exploratory and translational endpoints

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TRUST Endpoints and Statistical Design

- Primary endpoint was overall survival, calculated from the date of randomization.
- Secondary endpoints include progression-free survival, rate of complete tumor resection, surgical procedures, surgical morbidity and health related quality of life.
- A 1:1 randomization stratified by center and age-ECOG combination (ECOG 0 and age ≤65 years vs ECOG > 0 or age > 65 years) was performed.
- The primary endpoint overall survival was compared between the two treatment arms using a two-sided stratified log-rank test with significance level 0.05.
- **Observation of 380 deaths in eligible patients was calculated to provide a power of 80% assuming a hazard ratio of 0.75 in a test for superiority of PCS.**
- The planned sample size was 386 per arm to account for a drop-out rate of ~ 20%.

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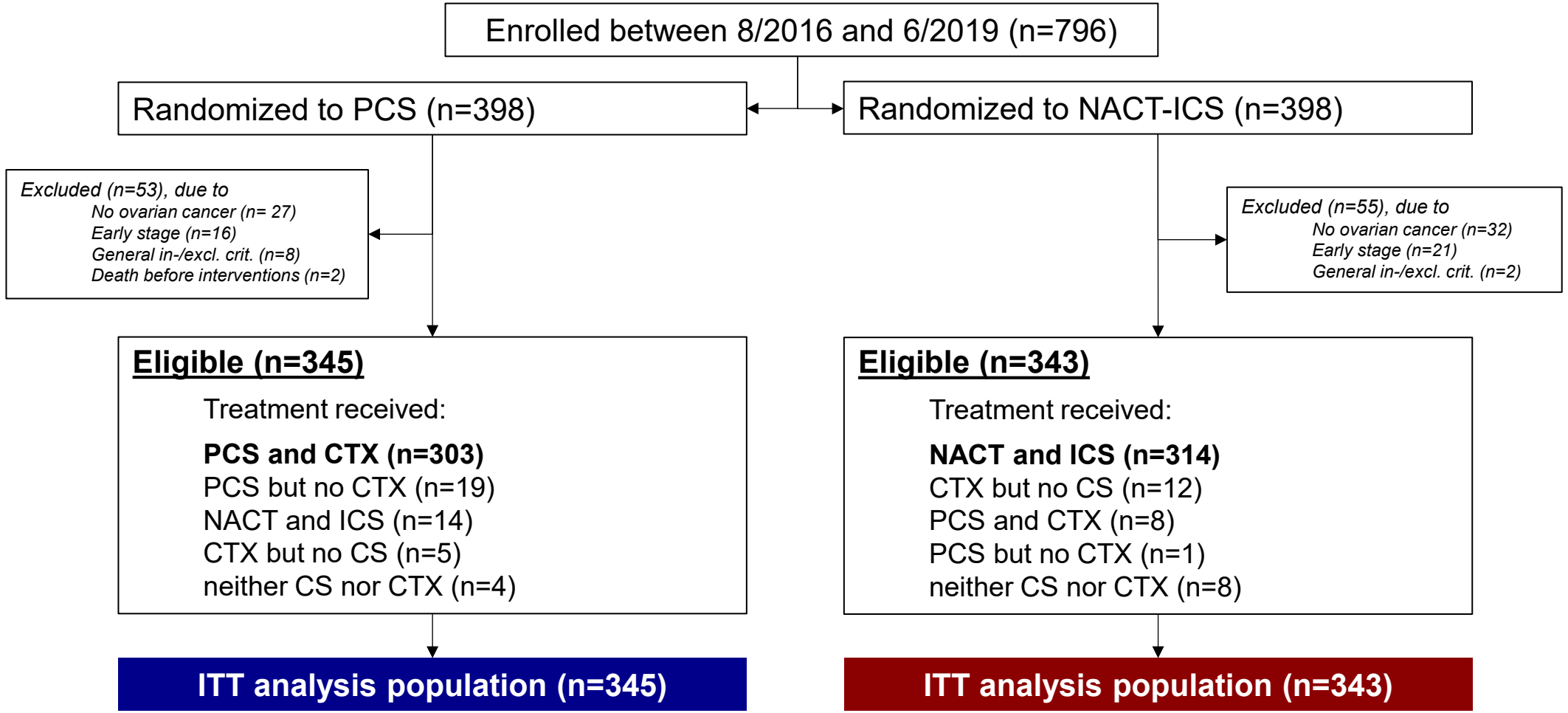
TRUST Patient Disposition



CS: Cytoreductive surgery; CTX: Chemotherapy; ITT: Intention-to-treat

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TRUST Baseline Characteristics

	PCS (n=345)	**NACT-ICS** (n=343)	**Total** (n=688)
Median age, years (range)	**63** (34-83)	**64** (32-83)	**63.5** (32-83)
Median BMI, kg/m^2 (range)	**24.6** (15.6-50.1)	**24.9** (15.9-47.2)	**24.8** (15.6-50.1)
ECOG, n (%)			
0	267 **(77%)**	263 **(77%)**	530 **(77%)**
1	78 **(23%)**	80 **(23%)**	158 **(23%)**
Confirmed FIGO stage (highest), n (%)			
IIIB	30 **(8.7%)**	18 **(5.3%)**	48 **(7.0%)**
IIIC	203 **(59%)**	217 **(63%)**	420 **(61%)**
IVA	31 **(9.0%)**	35 **(10%)**	66 **(9.6%)**
IVB	79 **(23%)**	68 **(20%)**	147 **(21%)**
Not reported	2 **(0.6%)**	5 **(1.5%)**	7 **(1.0%)**
Histological subtype, n (%)			
High grade serous	320 **(93%)**	312 **(91%)**	632 **(92%)**
Low grade serous	18 **(5.2%)**	23 **(6.7%)**	41 **(6.0%)**
Other*	4 **(1.2%)**	4 **(1.2%)**	8 **(1.2%)**
Not reported	3 **(0.9%)**	4 **(1.2%)**	7 **(1.0%)**

*Other: PCS: 3 endometrioid, 1 seromucinous; NACT-ICS: 2 clearcell, 1 seromucinous, 1 mucinous,

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TRUST Results: Surgical Effort and Procedures

Procedure, n* (%)	PCS (n=331)	NACT-ICS (n=328)
Median duration of surgery, minutes (IQR)	**331** (253-432)	**284** (213-360)
Median blood loss, mL (IQR)	**500** (300-800)	**400** (200-600)
Mean number of RBC units transfused (SD)	**0.9** (1.5)	**0.6** (1.1)
Upper abdominal procedures	263 **(79%)**	221 **(67%)**
Splenectomy	91 **(27%)**	42 **(13%)**
Intestinal resections	224 **(68%)**	123 **(38%)**
Colorectal resection	187 **(56%)**	95 **(29%)**
Large bowel resection	135 **(41%)**	74 **(23%)**
Small bowel resection	70 **(21%)**	33 **(10%)**
Stoma formation	66 **(20%)**	27 **(8.2%)**
Lymph node dissection	197 **(60%)**	156 **(48%)**
Pelvic nodes	166 **(50%)**	135 **(41%)**
Paraaortic nodes	172 **(52%)**	134 **(41%)**
Chest procedures	63 **(19%)**	35 **(11%)**
Pericardiophrenic nodes	33 **(10%)**	15 **(4.6%)**
Open assessment of the pleura	47 **(14%)**	23 **(7.0%)**
Pleurectomy	15 **(4.5%)**	5 **(1.5%)**

*. patients with documented debulking surgery; analyzed as treated;

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TRUST Results: Surgical Outcome

	PCS (n=345)	**NACT-ICS** (n=343)	**Total** (n=688)
Residual disease, n (%)			
complete gross resection	235 **(68%)**	271 **(79%)**	506 **(74%)**
macroscopic residual disease	99 **(29%)**	49 **(14%)**	148 **(22%)**
0.1-0.5 cm	*39 **(11%)***	*29 **(8.5%)***	*68 **(9.9%)***
0.6-1 cm	*25 **(7.3%)***	*7 **(2.0%)***	*32 **(4.7%)***
> 1 cm	*35 **(10%)***	*13 **(3.8%)***	*48 **(7.0%)***
not operated / not reported	11 **(3.2%)**	23 **(6.7%)**	34 **(4.9%)**
Documented complete resections in operated patients, n (%)	235/334 **(70%)**	271/320 **(85%)**	506/654 **(77%)**

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TRUST Results: Details on Systemic Therapy

Treatment n* (%)	PCS (n=345)	NACT-ICS (n=343)
First line chemotherapy	322 **(93%)**	334 **(97%)**
Platinum	322 **(93%)**	334 **(97%)**
Taxane	311 **(90%)**	330 **(96%)**
Bevacizumab treatment at any time	225 **(65%)**	201 **(59%)**
PARPi treatment at any time	86 **(25%)**	104 **(30%)**

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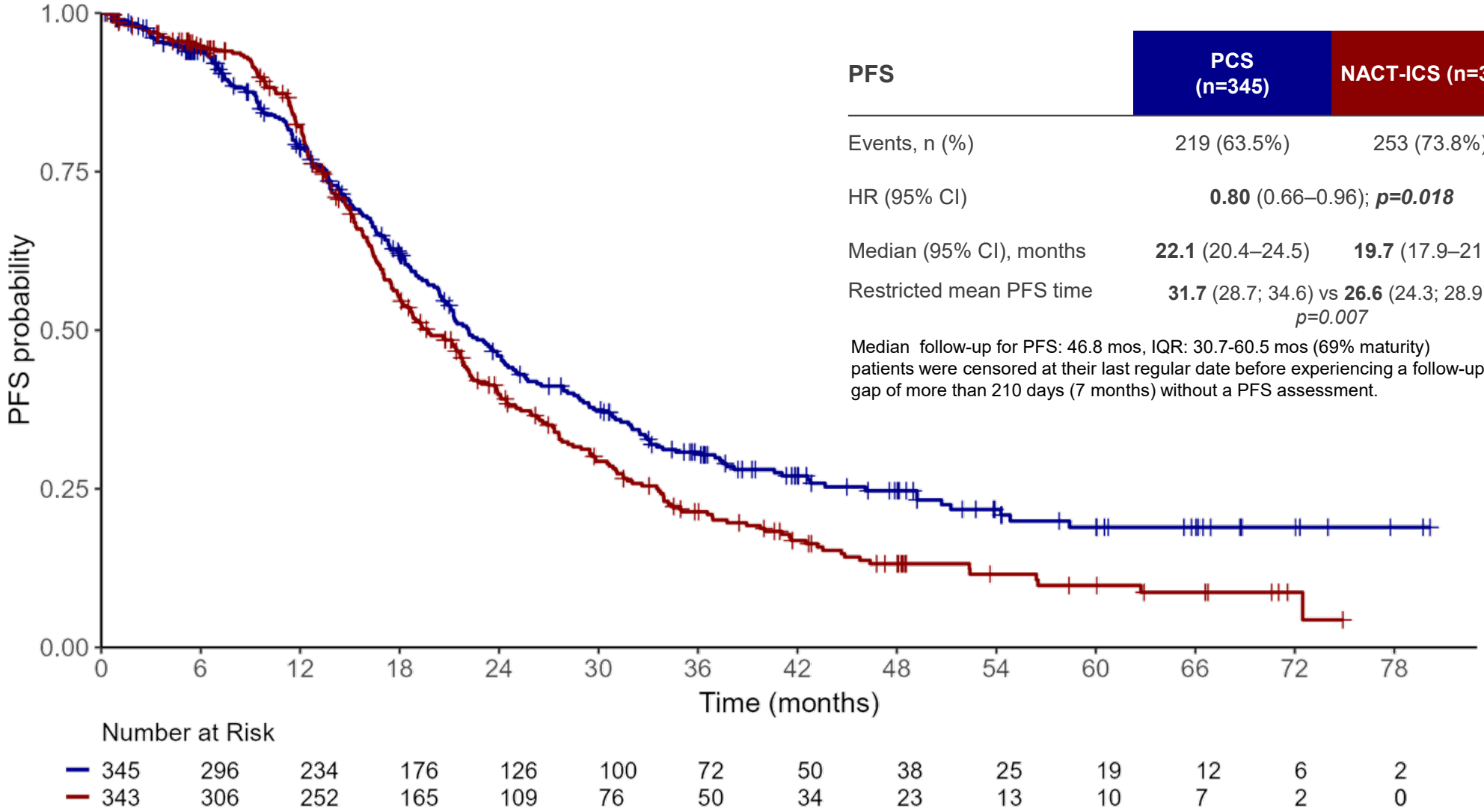
TRUST Results: Progression-free Survival (ITT)



PFS	PCS (n=345)	NACT-ICS (n=343)
Events, n (%)	219 (63.5%)	253 (73.8%)
HR (95% CI)	**0.80** (0.66–0.96); ***p=0.018***	
Median (95% CI), months	**22.1** (20.4–24.5)	**19.7** (17.9–21.9)
Restricted mean PFS time	**31.7** (28.7; 34.6) vs **26.6** (24.3; 28.9); *p=0.007*	

Median follow-up for PFS: 46.8 mos, IQR: 30.7-60.5 mos (69% maturity)
patients were censored at their last regular date before experiencing a follow-up gap of more than 210 days (7 months) without a PFS assessment.

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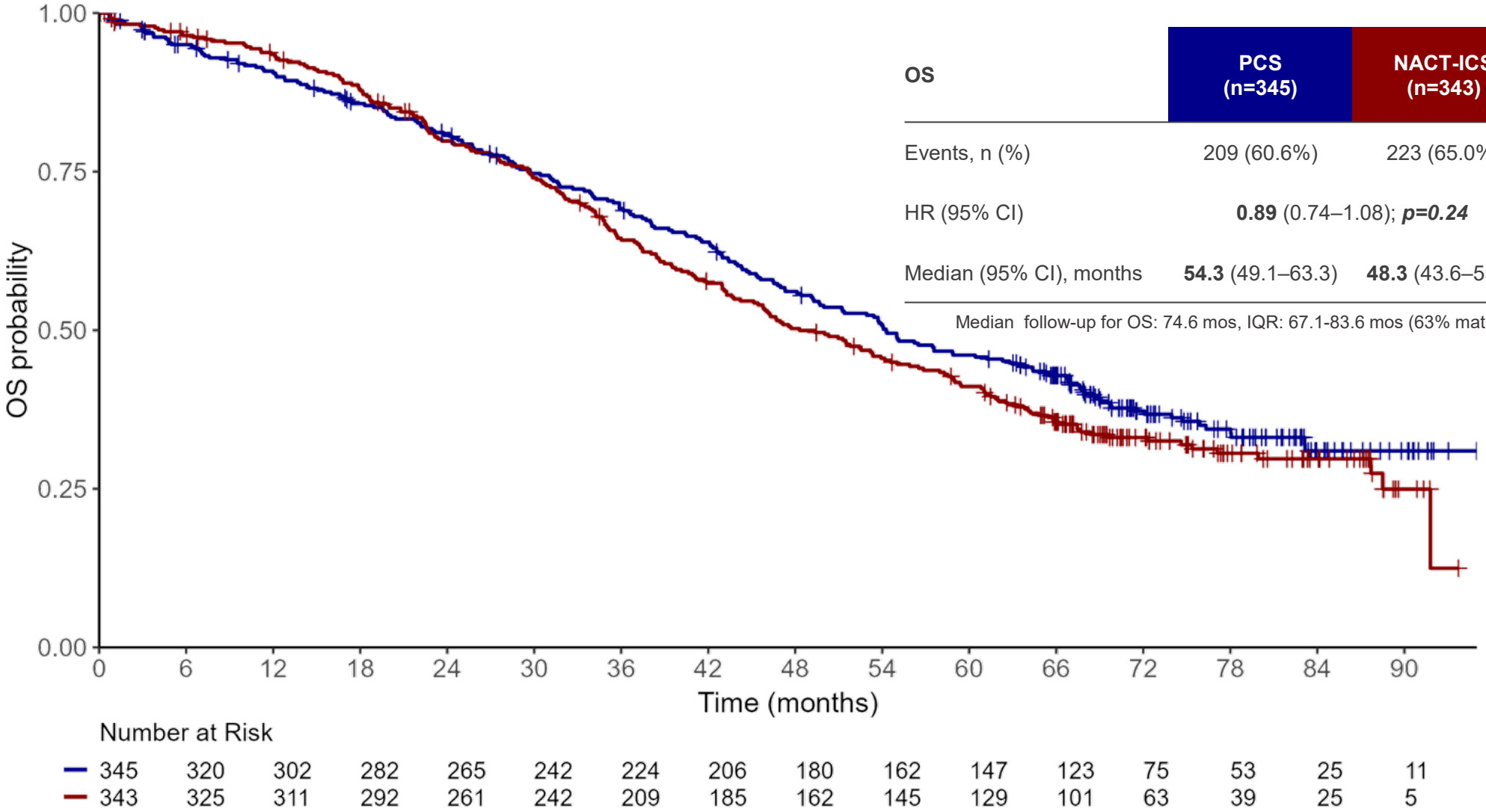
TRUST Results: Overall Survival (ITT)



OS	PCS (n=345)	NACT-ICS (n=343)
Events, n (%)	209 (60.6%)	223 (65.0%)
HR (95% CI)	**0.89** (0.74–1.08); ***p=0.24***	
Median (95% CI), months	**54.3** (49.1–63.3)	**48.3** (43.6–55.9)

Median follow-up for OS: 74.6 mos, IQR: 67.1-83.6 mos (63% maturity)

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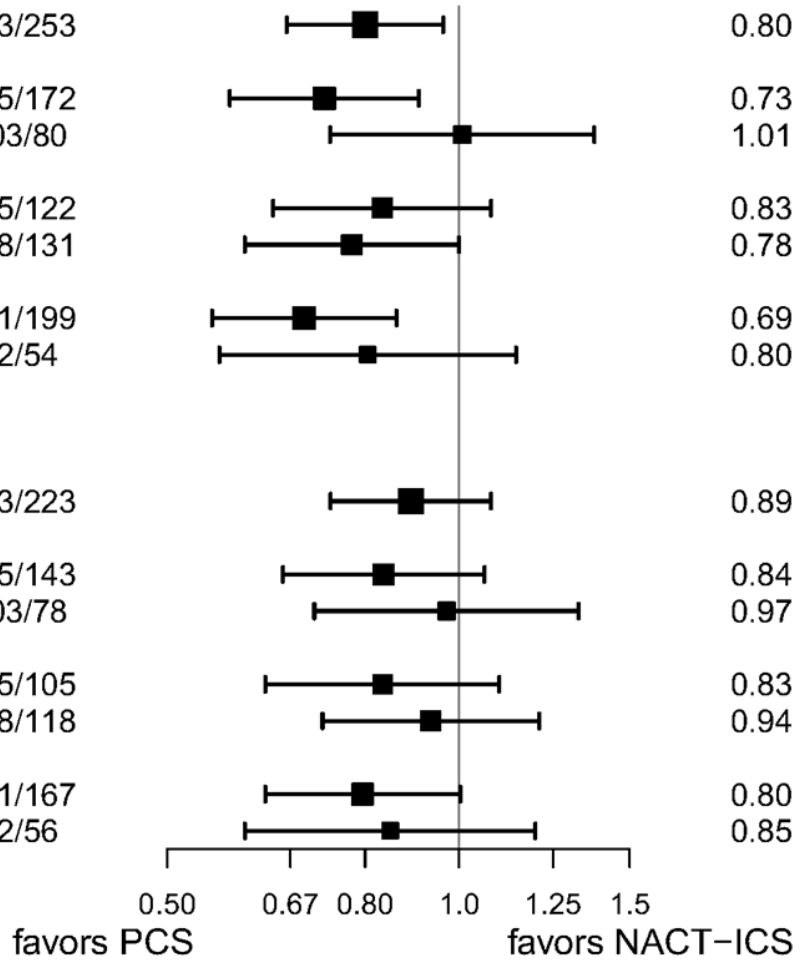
TRUST Results: Treatment Effects According to Subgroups

	PCS number/events	NACT-ICS number/events	Hazard Ratio	95% CI
PFS				
ITT	345/219	343/253	0.80	(0.66; 0.96)
FIGO III	232/140	235/172	0.73	(0.58; 0.91)
FIGO IV	110/79	103/80	1.01	(0.74; 1.38)
ECOG 0 AND age ≤ 65 yrs	171/110	175/122	0.83	(0.64; 1.08)
ECOG 1 OR age > 65 yrs	174/109	168/131	0.78	(0.60; 1.00)
Complete gross resection	235/137	271/199	0.69	(0.56; 0.86)
Macroscopic residual disease	110/82	72/54	0.80	(0.57; 1.15)
OS				
ITT	345/209	343/223	0.89	(0.74; 1.08)
FIGO III	232/127	235/143	0.84	(0.66; 1.06)
FIGO IV	110/81	103/78	0.97	(0.71; 1.33)
ECOG 0 AND age ≤ 65 yrs	171/95	175/105	0.83	(0.63; 1.10)
ECOG 1 OR age > 65 yrs	174/114	168/118	0.94	(0.72; 1.21)
Complete gross resection	235/126	271/167	0.80	(0.63; 1.00)
Macroscopic residual disease	110/83	72/56	0.85	(0.60; 1.20)



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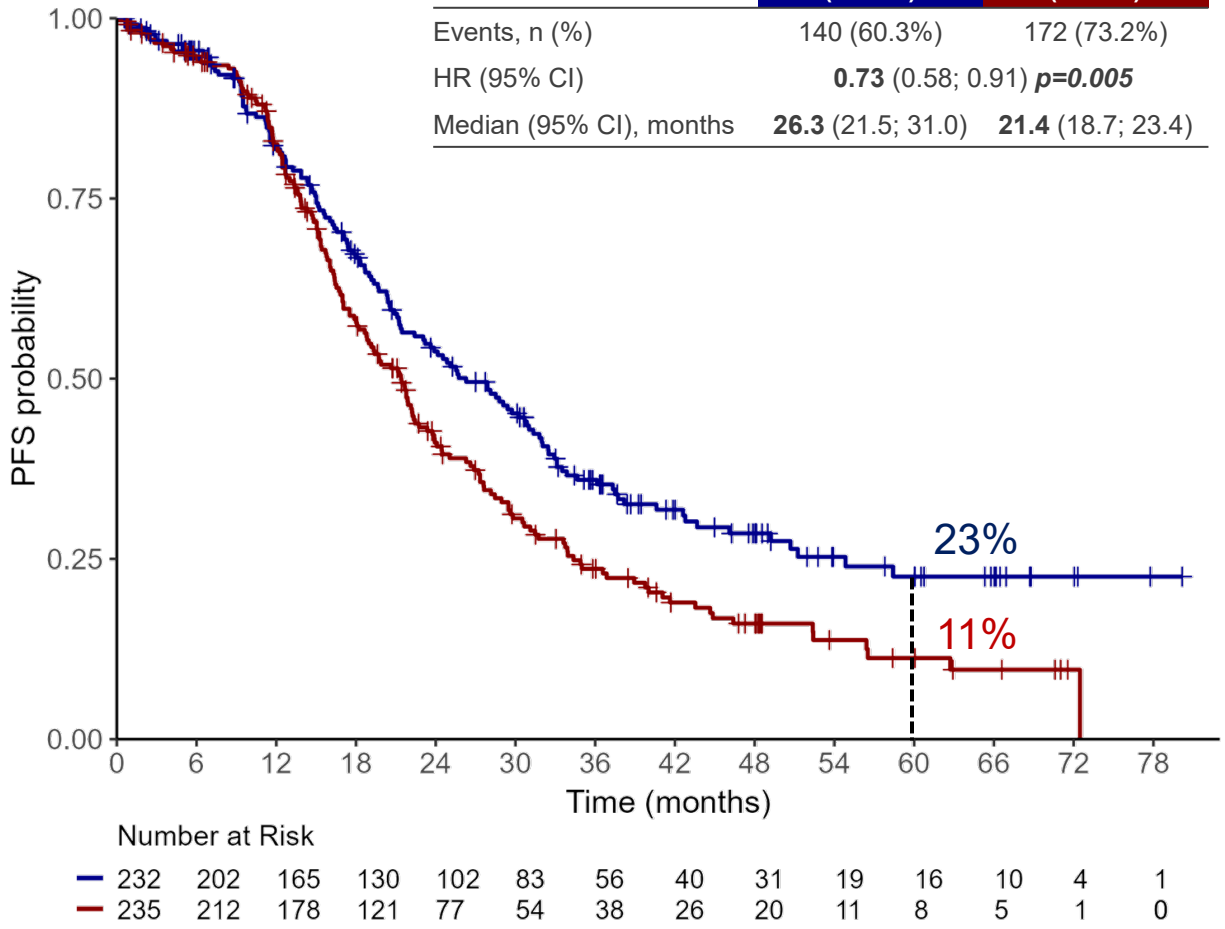
TRUST Results: Prespecified Exploratory Subgroup Analysis
FIGO Stage III

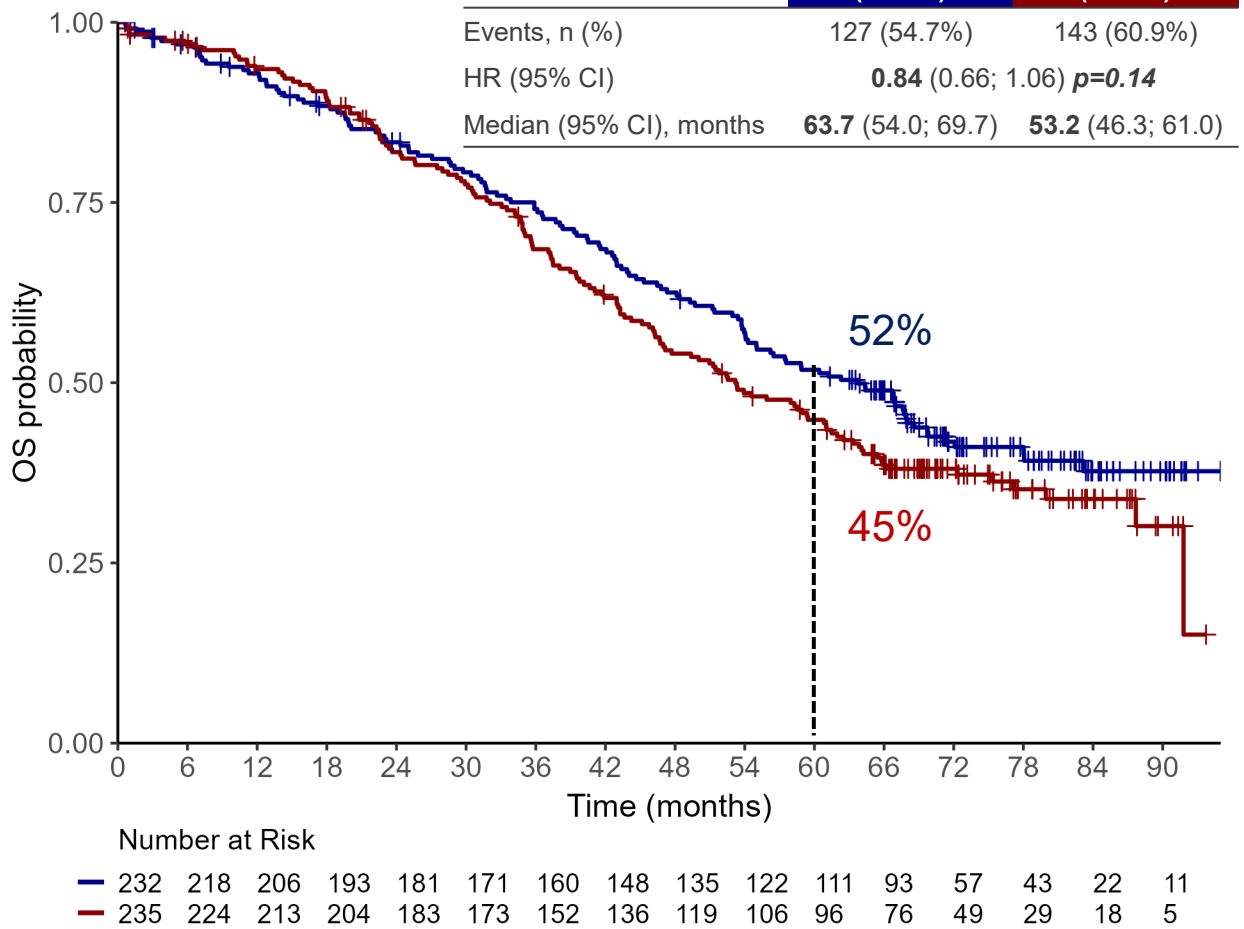
PFS

PFS	PCS (n=232)	NACT-ICS (n=235)
Events, n (%)	140 (60.3%)	172 (73.2%)
HR (95% CI)	**0.73** (0.58; 0.91) ***p=0.005***	
Median (95% CI), months	**26.3** (21.5; 31.0)	**21.4** (18.7; 23.4)



OS

OS	PCS (n=232)	NACT-ICS (n=235)
Events, n (%)	127 (54.7%)	143 (60.9%)
HR (95% CI)	**0.84** (0.66; 1.06) ***p=0.14***	
Median (95% CI), months	**63.7** (54.0; 69.7)	**53.2** (46.3; 61.0)



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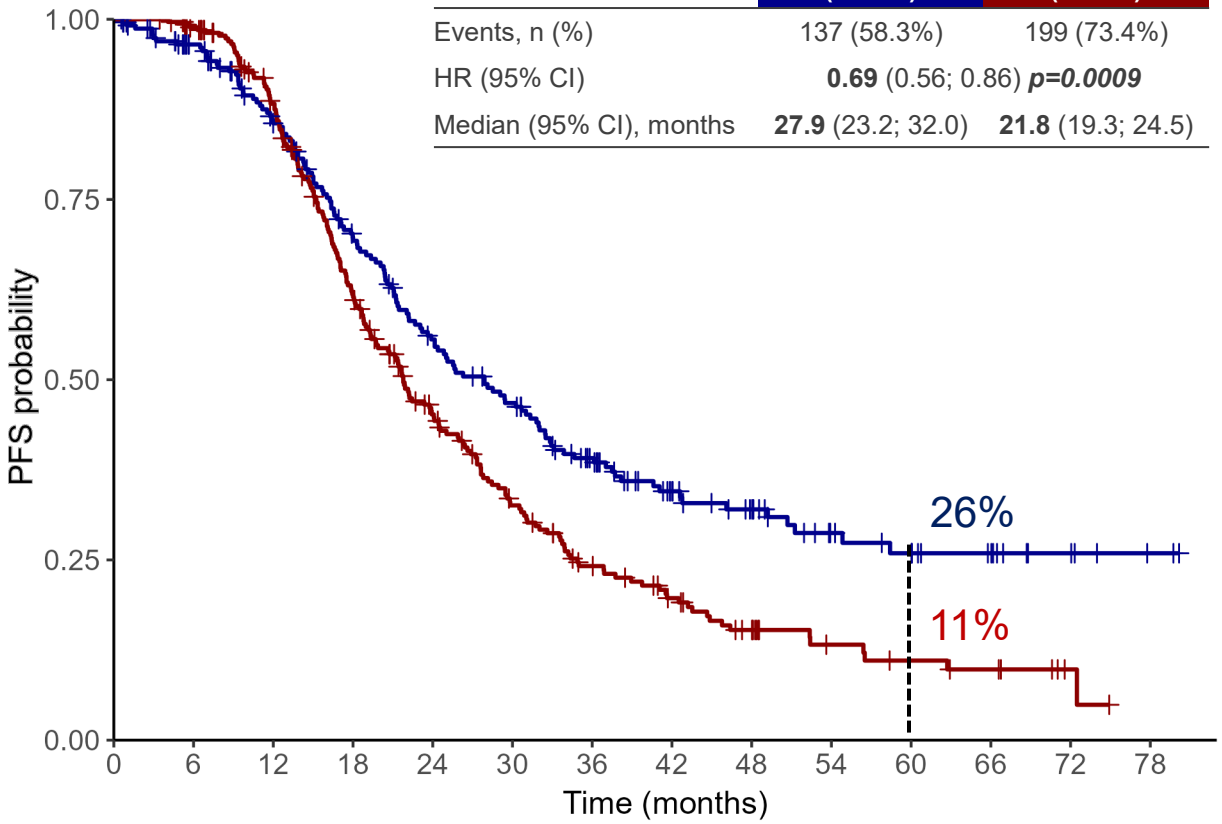
TRUST Results: Prespecified Exploratory Subgroup Analysis
Complete Gross Resection in All FIGO Stages

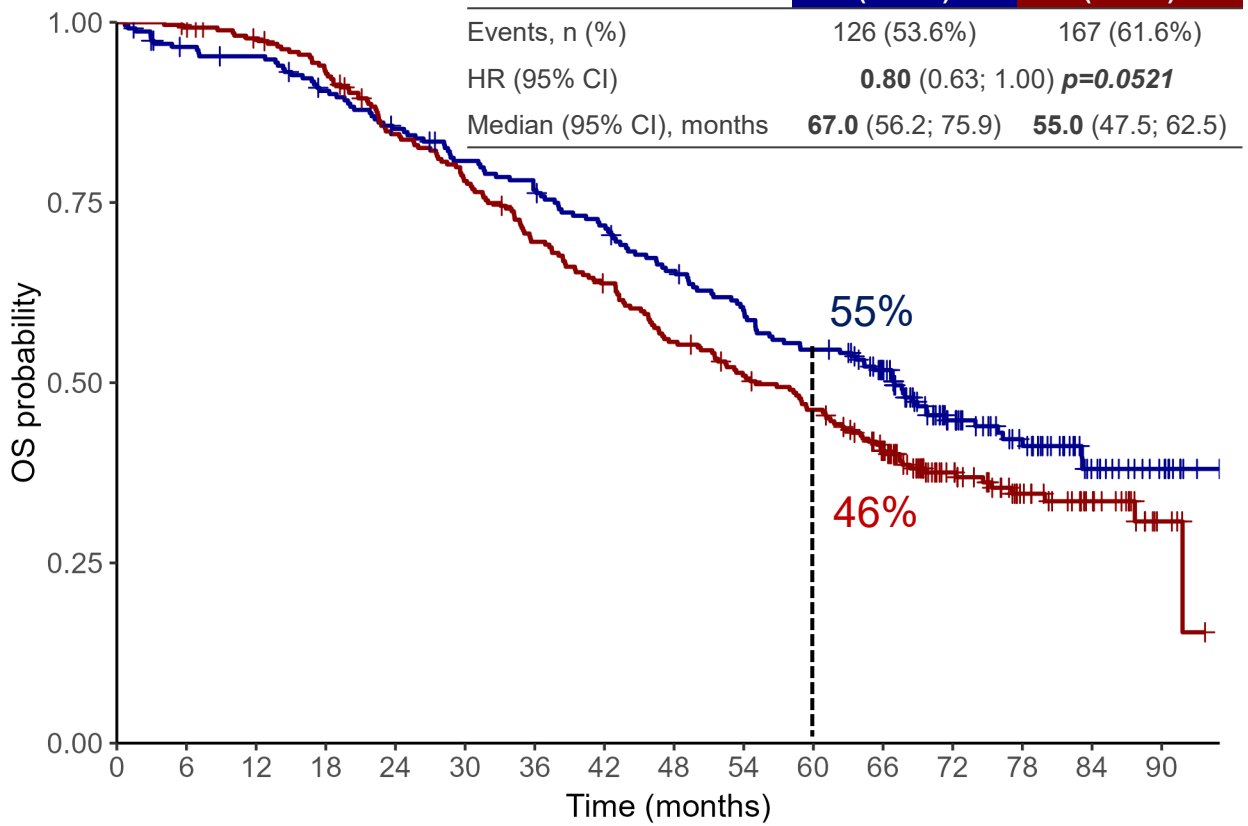
PFS

PFS	PCS (n=235)	NACT-ICS (n=271)
Events, n (%)	137 (58.3%)	199 (73.4%)
HR (95% CI)	**0.69** (0.56; 0.86) ***p=0.0009***	
Median (95% CI), months	**27.9** (23.2; 32.0)	**21.8** (19.3; 24.5)



OS

OS	PCS (n=235)	NACT-ICS (n=271)
Events, n (%)	126 (53.6%)	167 (61.6%)
HR (95% CI)	**0.80** (0.63; 1.00) ***p=0.0521***	
Median (95% CI), months	**67.0** (56.2; 75.9)	**55.0** (47.5; 62.5)



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TRUST Results: Surgical Morbidity

Complication, n* (%)	PCS (n=331)	NACT-ICS (n=328)
Any complication	60 (**18%**)	39 (**12%**)
>10 packed red blood cells within 24h	0	0
30-day post-op mortality	3 (**0.9%**)	2 (**0.6%**)
Re-laparotomy	21 (**6.3%**)	12 (**3.7%**)
Wound breakdown	11 (**3.3%**)	11 (**3.4%**)
Deep venous thrombosis	3 (**0.9%**)	1 (**0.3%**)
Pulmonary embolism	5 (**1.5%**)	3 (**0.9%**)
Sepsis	6 (**1.8%**)	4 (**1.2%**)
Anastomotic leak / fistula	11 (**3.3%**)	7 (**2.1%**)
Intraabdominal abscess	2 (**0.6%**)	1 (**0.3%**)
Nerve damage	1 (**0.3%**)	3 (**0.9%**)
Liver/renal failure	6 (**1.8%**)	2 (**0.6%**)
Serious cardiovascular event	8 (**2.4%**)	1 (**0.3%**)
Readmittance b/o any other complication	11 (**3.3%**)	5 (**1.5%**)

*. patients with documented cytoreductive surgery; analyzed as treated; complications that occurred within 28 days of debulking surgery

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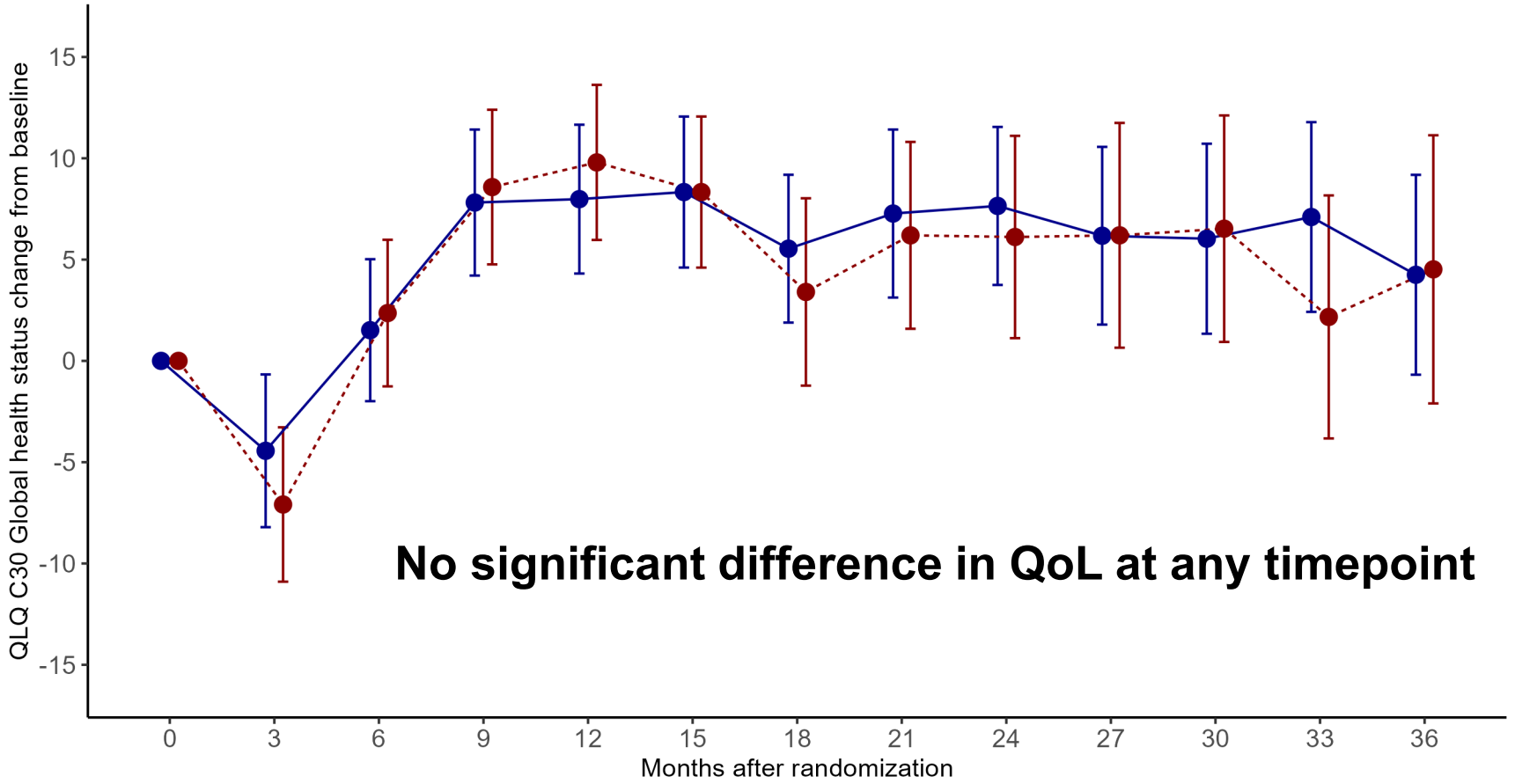
TRUST Results: Overall Quality of Life



PCS	291	184	220	193	191	182	161	165	146	143	123	115	100
NACT-ICS	293	241	226	203	205	182	169	156	139	121	106	96	83

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TRUST Conclusions

- The primary endpoint of the study, a statistically significant OS improvement after primary versus interval cytoreductive surgery, was not met.
- TRUST is the first randomized phase III trial to show a benefit in median PFS for primary over interval cytoreductive surgery without compromising short- or long-term quality of life.
- Observed benefits were linked to high complete resection rates, reinforcing the value of radical upfront surgery in pts with resectable advanced ovarian cancer.
- The high rate of complete cytoreduction with low morbidity and mortality along with excellent PFS and OS emphasize the importance of surgical quality assurance programs.

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