PÓS 2017 ASCO ANNUAL MEETING

Making a Difference in Cancer Care *WITH YOU*

Grupo ONCOCLÍNICAS
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Tumores Ginecológicos

Apresentação

A Sociedade Americana de Oncologia Clínica (ASCO) foi fundada em 1964 e, desde então, tornou-se a principal organização voltada para profissionais que lidam diariamente com o câncer em todo o mundo.

Sua missão é promover o combate à doença, habilitando seus membros a oferecer o que existe de melhor em termos de tratamento para o seus pacientes. Para isso, investe maciçamente em pesquisa e é reconhecida por promover educação continuada de alto nível.

Todos os anos, a ASCO organiza seu Congresso, reunindo os mais renomados profissionais do mundo em todas as áreas da Oncologia. O contato direto com profissionais de destaque, o intenso compartilhamento de informações, assim como a troca de experiências cotidianas criam um ambiente favorável para o aprendizado.

O Grupo Oncoclínicas não poderia deixar de estar presente nesse evento, trazendo para seus pacientes e parceiros todas as novidades apresentadas. Em linha com nosso objetivo de nos transformar no melhor grupo de Oncologia do país, estivemos presentes com mais de 80 Oncologistas em Chicago, coletando os principais e mais atualizados dados científicos.

E por meio do Instituto Oncoclínicas conseguimos compilar as informações mais relevantes, transformando-as em um *slide kit* didático, versátil e inovador. É com prazer que disponibilizamos a vocês, nossos parceiros, o “Melhor da ASCO 2017”.

Instituto Oncoclínicas

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CONFLITOS DE INTERESSE

Esses slides estão isentos de conflitos de interesses e possuem finalidade essencialmente educacional.

ROTEIRO

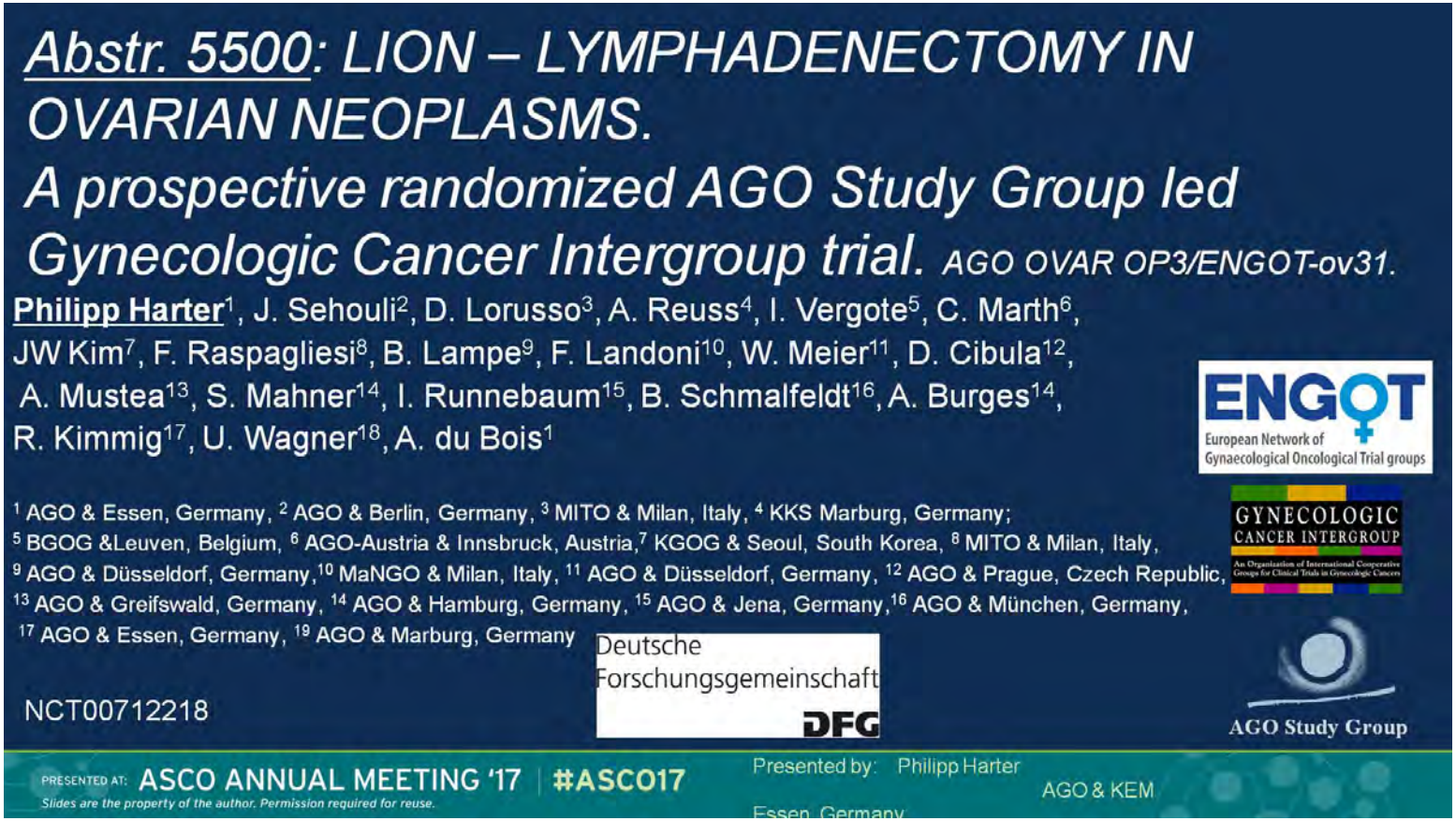
1. Câncer de Ovário
   - Existe papel para linfadenectomia profilática?
   - Qual o papel da cirurgia Citorredutora secundária na recorrência?
   - Olaparibe de manutenção: Qual o impacto na Qualidade de vida?
   - Há papel para Bevacizumabe Neoadjuvante em pacientes que farão cirurgia de intervalo?

2. Câncer de Endométrio
   - Resultados finais do PORTEC-3
   - QT/RT versus apenas QT em Câncer de endométrio localmente avançado otimamente operado
   - Taxanes com platinas *vs* Adriamicina com platina no tratamento adjuvante do Ca de endométrio de alto risco

3. Câncer de colo uterino, vagina e vulva
   - Nivolumabe em Câncer de colo uterino, vagina e vulva recorrentes/ metastáticos

Câncer de Ovário

Existe papel para linfadenectomia profilática no Câncer de ovário?



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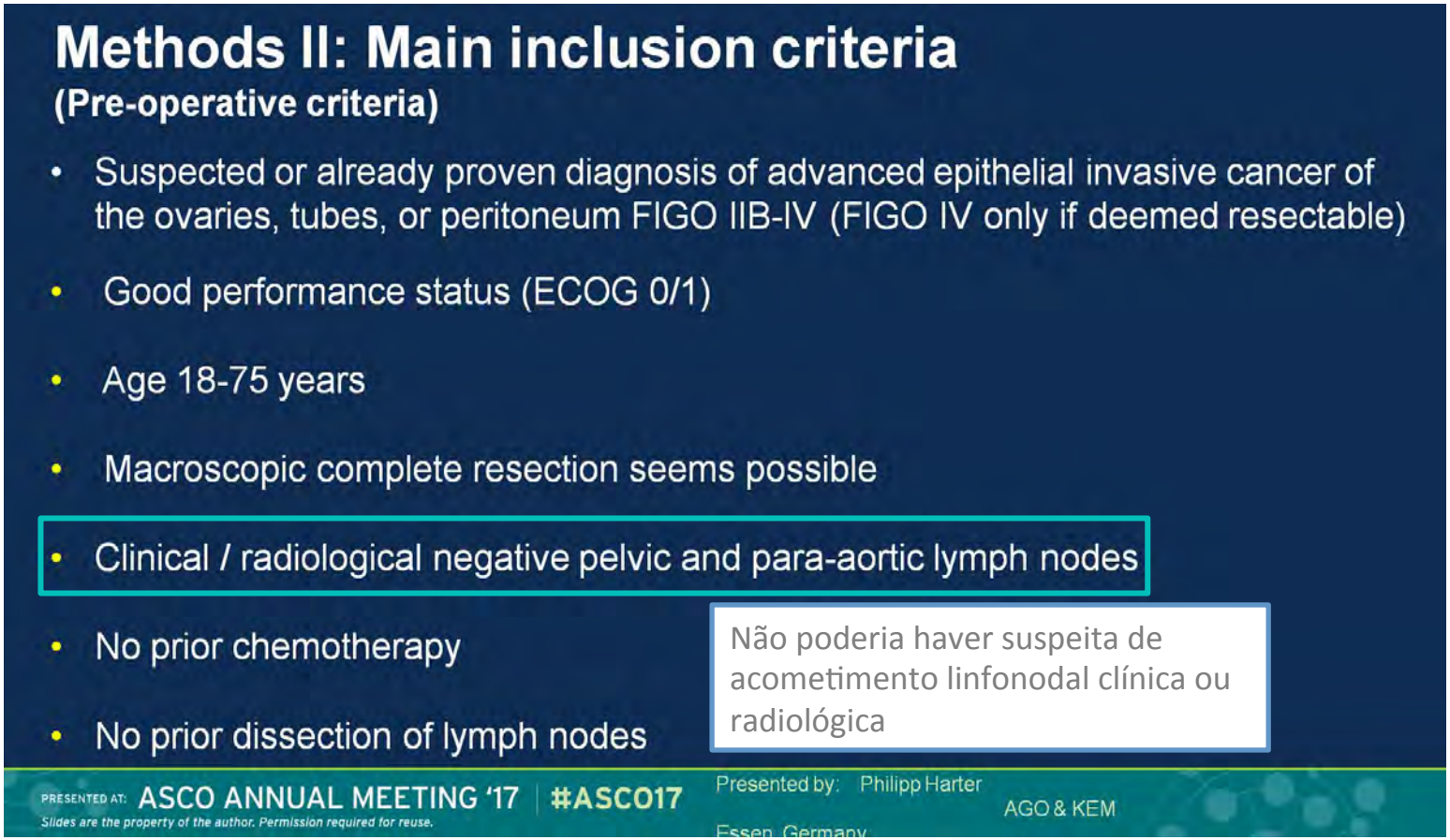
LION trial



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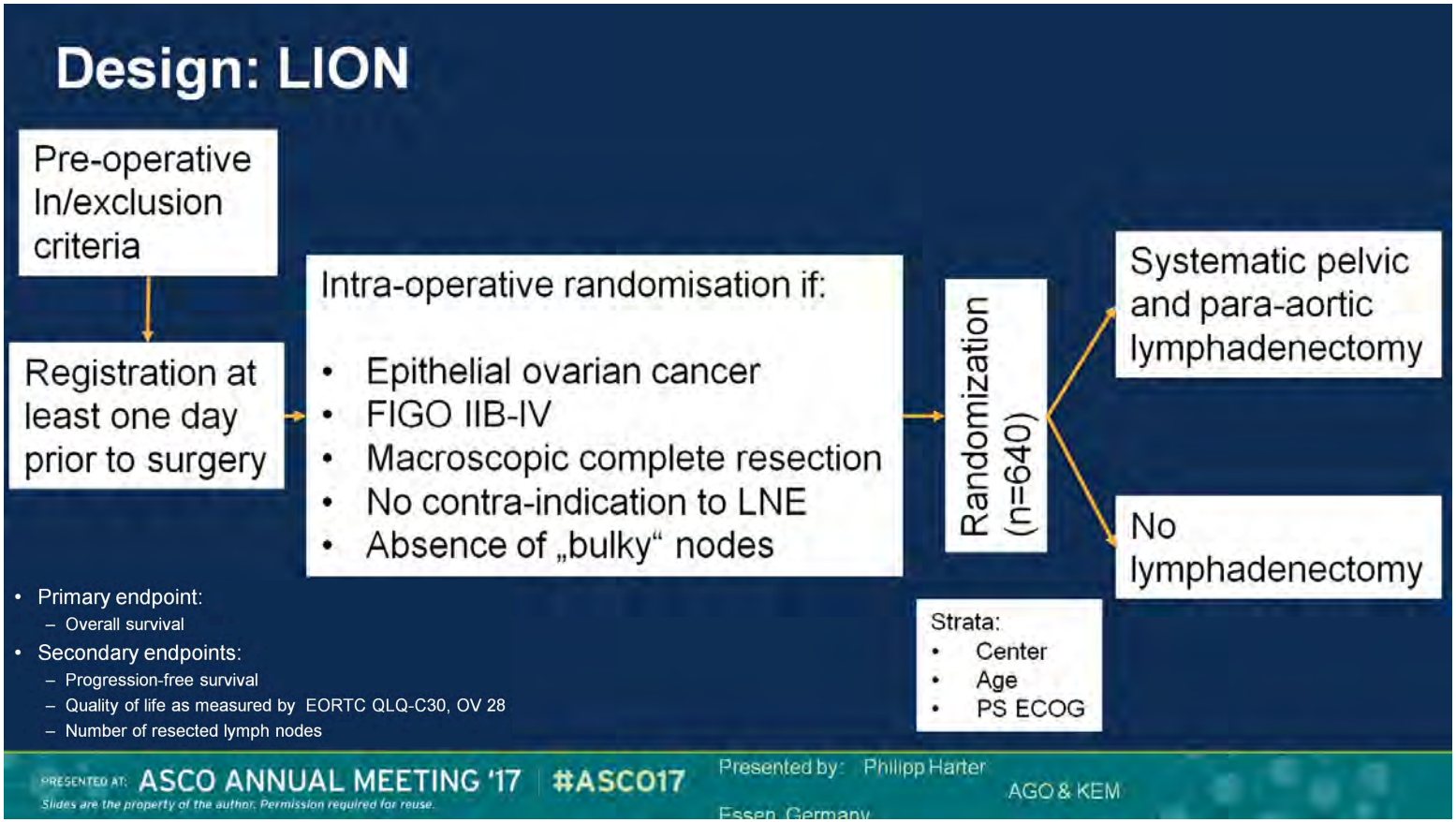
LION trial



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LION trial

LION: Patient characteristics

	LNE (%), n= 323	No LNE (%), n=324	P-value
Age (median, range) [years]	60 (21-83)	60 (23-78)	0.66
Performance status ECOG 0 ECOG 1	 272 (84.2) 51 (15.8)	 280 (86.4) 44 (13.6)	0.43
Histologic diagnosis before registration	106 (32.8)	106 (32.7)	0.98
CA 125 pre-OP (median, IQR) [U/ml]	416 (138-1276)	347 (122-1025)	0.42
Final histological diagnosis Ovarian / Fallopian Tube / Peritoneal Ca Others	 304 (94.1) 19 (5.9)	 303 (93.5) 21 (6.5)	0.75
Final FIGO stage* I-IIA IIB-IIIA III-IV missing	 15 (4.6) 41 (12.7) 261 (80.8)** 6 (1.9)	 17 (5.2) 52 (16.0) 244 (75.3)*** 11 (3.4)	0.32
Histology: G2/3 serous others	 234 (72.4) 89 (27.6)	 227 (70.1) 97 (29.9)	0.54

Os grupos estavam bem balanceados

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LION trial

LION: Characteristics of surgery

	LNE (%)	No LNE (%)	P-value
Bilateral Salpingo-oophorectomy*	319 (98.8)	320 (98.8)	0.99
Hysterectomy*	321 (99.4)	322 (99.4)	0.99
Omentectomy	319 (98.8)	322 (99.4)	0.41
(Partial) peritonectomy • Pelvis • Paracolic • Diaphragm	291 (90.1) 276 (85.5) 193 (59.8) 173 (53.6)	291 (89.8) 278 (85.8) 208 (64.2) 196 (60.5)	0.99
Gastrointestinal tract resection Stoma	169 (52.3) 34 (10.5)	167 (51.5) 24 (7.4)	0.84 0.17
Splenectomy	62 (19.2)	56 (17.3)	0.53
Porta hepatis/lesser omentum	61 (18.9)	69 (21.3)	0.44
Partial pancreatectomy Partial hepatectomy Pleurectomy	7 (2.1) 27 (8.4) 20 (6.2)	7 (2.1) 28 (8.6) 24 (7.4)	0.99 0.90 0.54
Complete resection	321 (99.4)	322 (99.4)	0.99

* Including earlier performed

Os procedimentos cirúrgicos foram os mesmos em ambos os grupos

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LION trial

LION: Characteristics of surgery

	LNE (%)	No LNE (%)	Difference	p-value
Study procedure according to randomisation	320 (99.1)	313 (96.6)		
Resected LN total (median, IQR) Para-aortic LN Pelvic LN	57 (45-73) 22 (16-33) 35 (26-43)			
Lymph node metastases	180 (55.7)			
Duration (median, IQR) [min]	340 (270-420)	280 (210-360)	+ 1 hour	<0.001
Blood loss (median, IQR) [ml]	650 (400-1000)	500 (300-900)	+ 150 ml	<0.001
Transfusions Massive transfusions (> 10 RBC/24h)	205 (63.7) 7 (2.2)	181 (56.0) 2 (0.6)	+ 8%	0.005 0.09
Fresh-frozen plasma	117 (36.3)	96 (29.7)	+ 7%	0.07
Intermediate/Intensive Care Unit	250 (77.6)	223 (69.4)	+ 8%	0.01

Metástases linfonodais foram identificadas em 55,7% dos casos!!!

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LION trial

LION: Post-surgical outcome

	LNE (%)	No LNE (%)	p-value
Infections requiring antibiotics	83 (25.8)	60 (18.6)	0.03
Fever > 38.0° Celsius	41 (12.7)	32 (9.9)	0.21
Sepsis	6 (1.9)	3 (0.9)	0.31
Thrombosis	7 (2.2)	5 (1.6)	0.56
Pulmonary embolism	12 (3.7)	15 (4.6)	0.56
Secondary wound healing	31 (9.6)	19 (5.9)	0.12
Prolonged ileus (conservative management)	15 (4.6)	17 (5.3)	0.72
Peripheral sensoric neurologic event	7 (2.2)	7 (2.2)	0.99
Peripheral motoric neurologic event	10 (3.1)	8 (2.5)	0.63
Asymptomatic lymph cysts	14 (4.4)	1 (0.3)	<0.001
Symptomatic lymph cysts	10 (3.1)	0	0.001
Fistula	5 (1.6)	7 (2.2)	0.56
Readmission rate	40 (12.4)	27 (8.3)	0.09
Rate of re-laparotomy for complications	40 (12.4)	21 (6.5)	0.01
60 day postoperative mortality	10 (3.1)	3 (0.9)	0.049
Platinum + Taxan i.v.	257 (79.6)	274 (84.6)	0.09

Foram observadas mais complicações no grupo de Linfadenectomia

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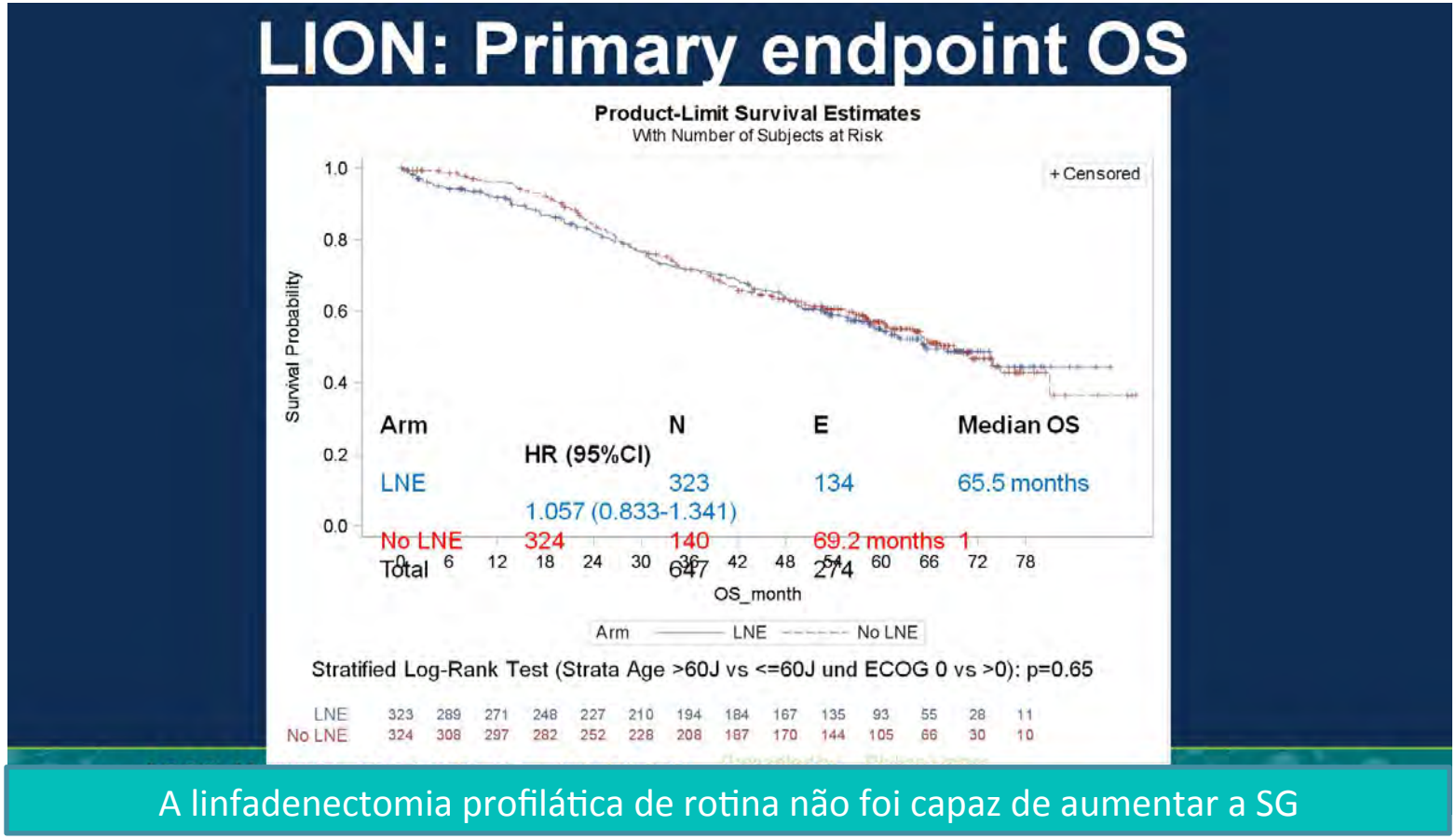
LION trial



A linfadenectomia profilática de rotina não foi capaz de aumentar a SG

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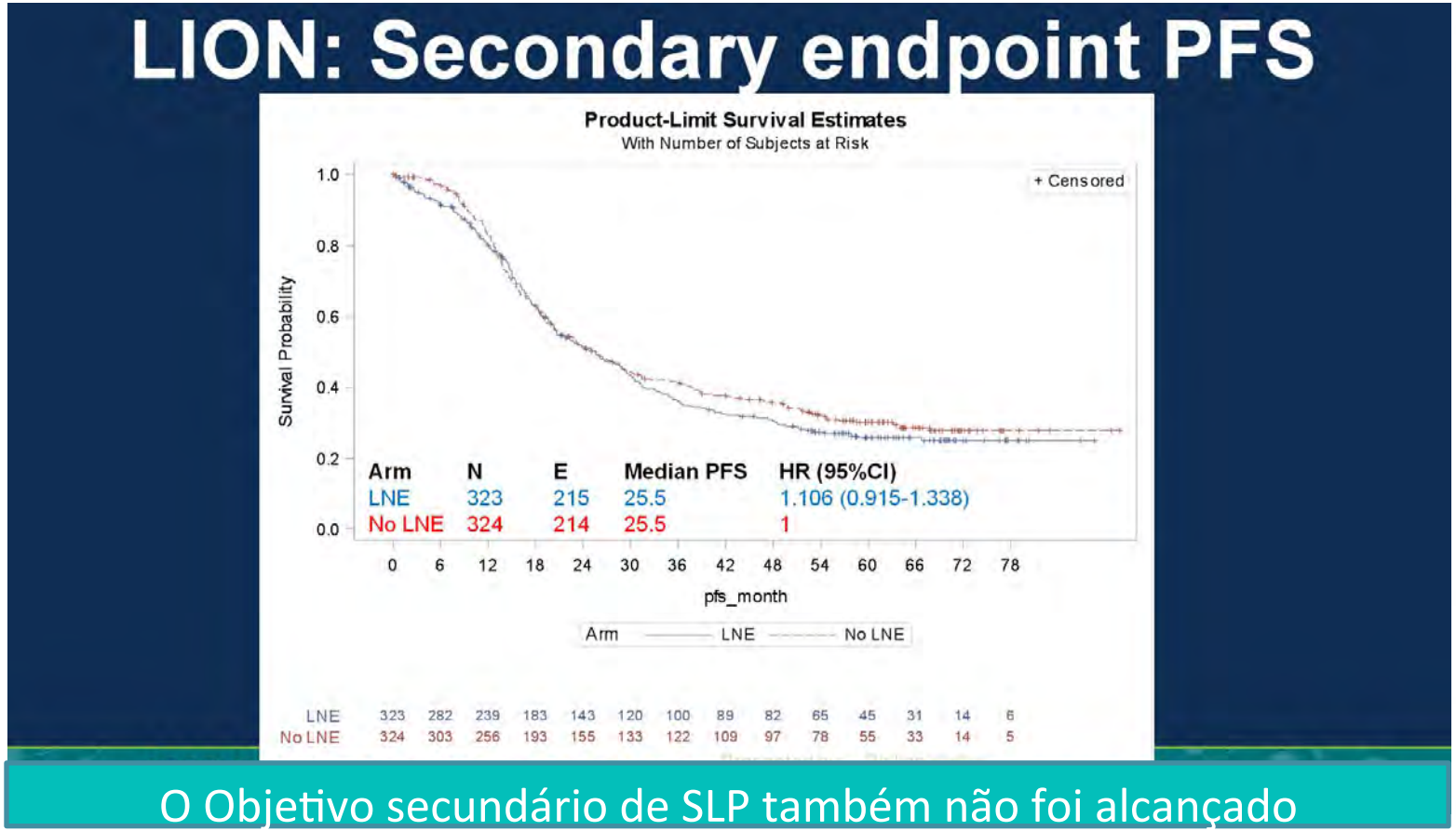
LION trial



O Objetivo secundário de SLP também não foi alcançado

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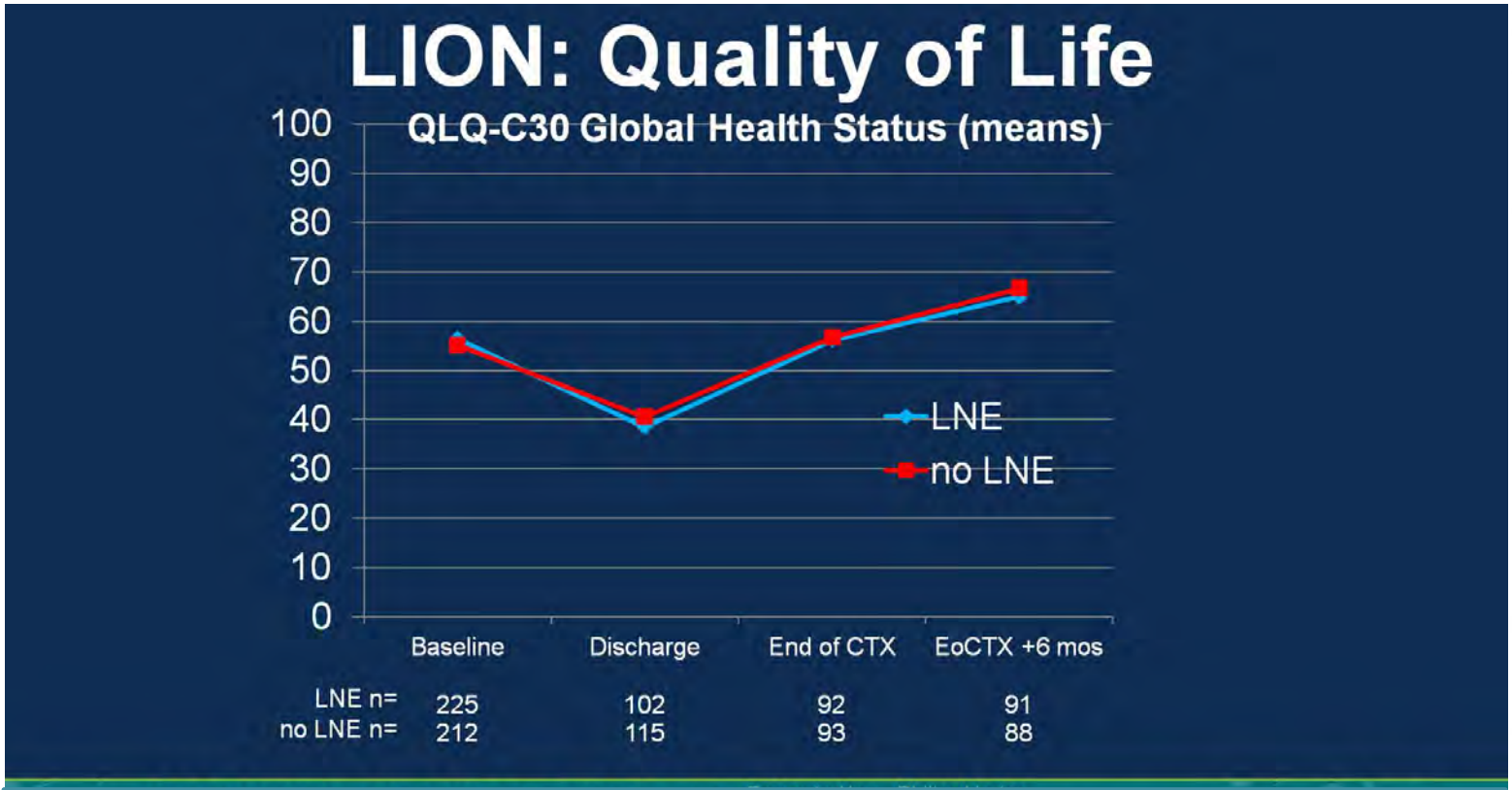
LION trial



De forma geral, a Qualidade de vida não foi afetada pela Linfadenectomia

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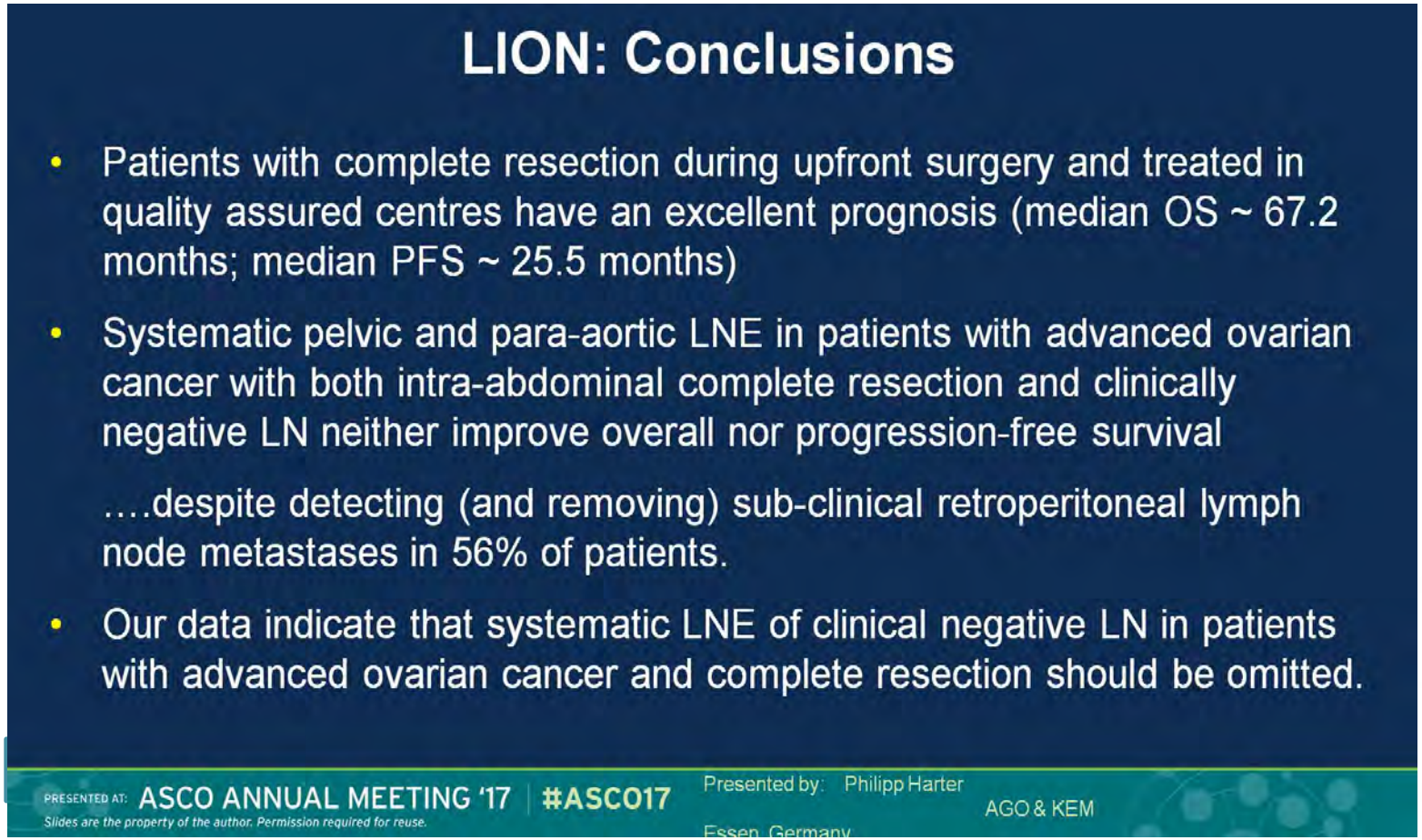
LION trial



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Qual o papel da cirurgia Citorredutora secundária no Ca de ovário recorrente?

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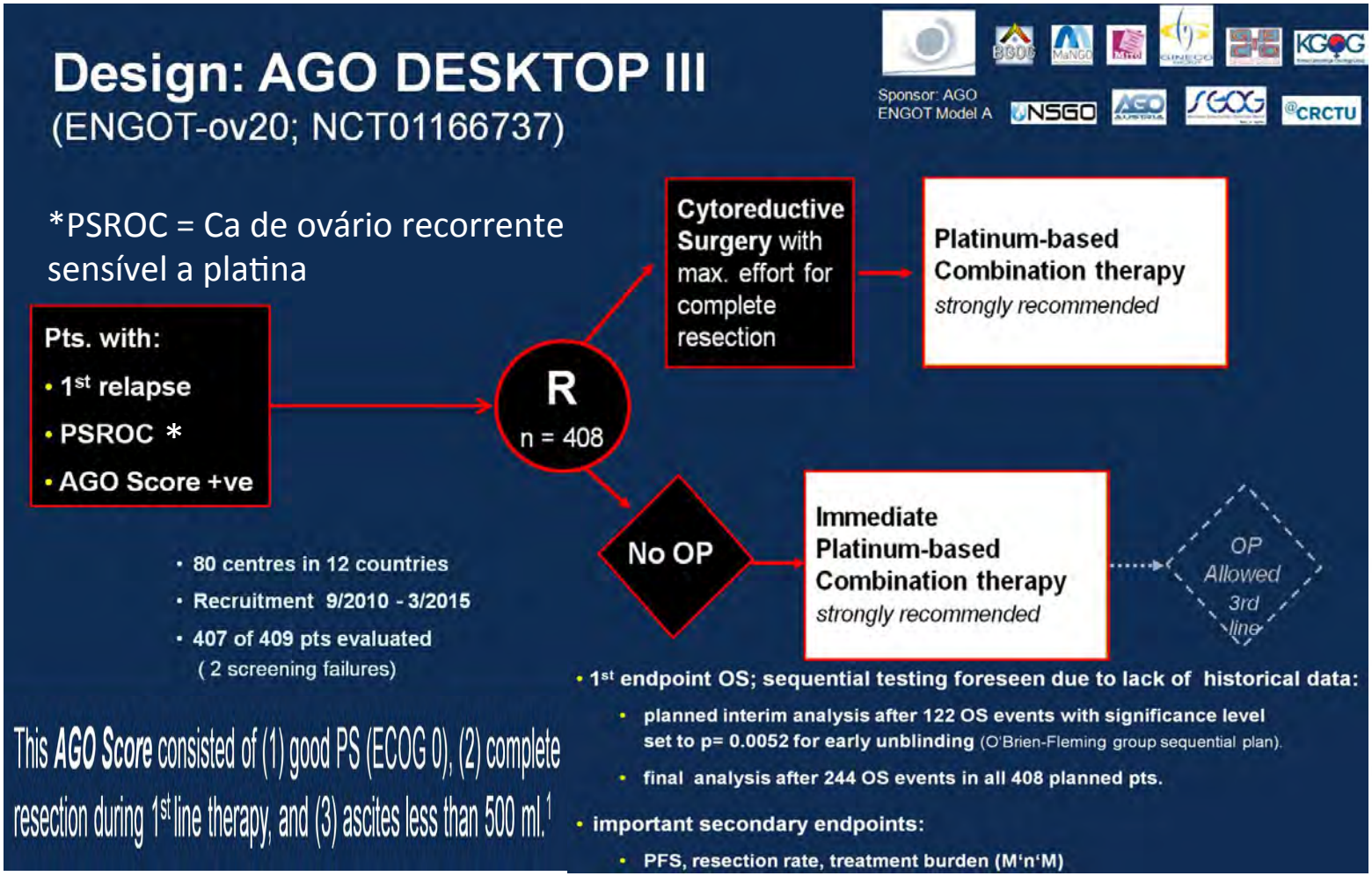
DESKTOP 3 *trial*



DESKTOP 3 *trial*

AGO DESKTOP III: Patients' Characteristics

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	No surgery	Surgery	P-value
Pts. (n)	203	204	
Age (median, yrs)	62.2	60.7	0.24
Initial FIGO stage IIIB-IV	149 (73.4%)	152 (74.9%)	0.73
Histology G2/3 serous	**157 (77.3%)**	**171 (83.8%)**	0.11
No prior chemo	2 (1.0%)	2 (1.0%)	0.57
Prior platinum w/o taxan	16 (7.9%)	10 (4.9%)	
Prior platinum + taxan	**182 (89.7%)**	**191 (93.6%)**	
Pt-free-Int. > 12 months	152 (74.9%)	155 (76.0%)	0.80
Median Pt-free-Interval	**18.7 months**	**21.1 months**	0.39

Os dois grupos estavam bem balanceados

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DESKTOP 3 *trial*

AGO DESKTOP III: Therapy after Randomisation
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	No surgery	Surgery	P-value
Non compliant with random arm	**8 (3.9%) with OP**	**12 (5.9%) w/o OP**	0.36
Post-random chemotherapy:			
Platinum containing therapy	**185 (91.1%)**	**181 (88.7%)**	
Non-platinum	6 (3.0%)	5 (2.5%)	0.51
None / missing data	12 (5.9%)	18 (8.8%)	
Bevacizumab	45 (22.2%)	38 (18.6%)	0.32
PARP Inhibitors	1 (0.5%)	0 (0%)	0.25
Post-event surgery after 2nd relapse (within 3 mos after 2nd relapse)	**20 (11%)**	**9 (5.4%)**	0.09

1) A maioria dos pacientes recebeu QT a base de platina, em ambos os grupos.
2) Uma minoria dos pacientes, em ambos os grupos, ainda recebeu nova cirurgia após 2ª recorrência

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DESKTOP 3 *trial*

AGO DESKTOP III: Surgery arm

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

Duration of surgery (minutes; median / quartiles)	220 (150 – 300)
Bowel resection	33.2%
Stoma diversion temporary / permanent	3.5% / 3.5%
Blood loss (ml; median / quartiles)	250 (50 – 500)
RBC transfusion	20.3%
Fever > 38°C	4.8%
Antibiotic treatment (mainly for urinary tract infections)	19.0%
Peri-OP thrombosis	1.1%
Re-laparotomy rate	3.2%
Macroscopic complete resection rate	**72.5%**

72,5% dos pacientes receberam ressecção macroscópica total (dentro do esperado)

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DESKTOP 3 *trial*

AGO DESKTOP III: Outcome 1 (1st endpoint OS)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

- The observed pooled 2-YSR was 83% and much higher than the assumed 2-YSR in the overall trial population.
- According to the trial protocol a planned interim analysis took place after observation of 122 OS events. This analysis did not reach the local significance level which was set to alpha=0.0052 for a two-sided test.*
- The blinded data were presented to the IDMSC which recommended that follow-up should continue until observation of the planned 244 events for the final OS analysis which will need app. 2x yrs. maturation.

83% dos pacientes estavam vivos após 2 anos, o que foi surpreendentemente melhor do que o planejado. Assim, os dados de SG estão imaturos.

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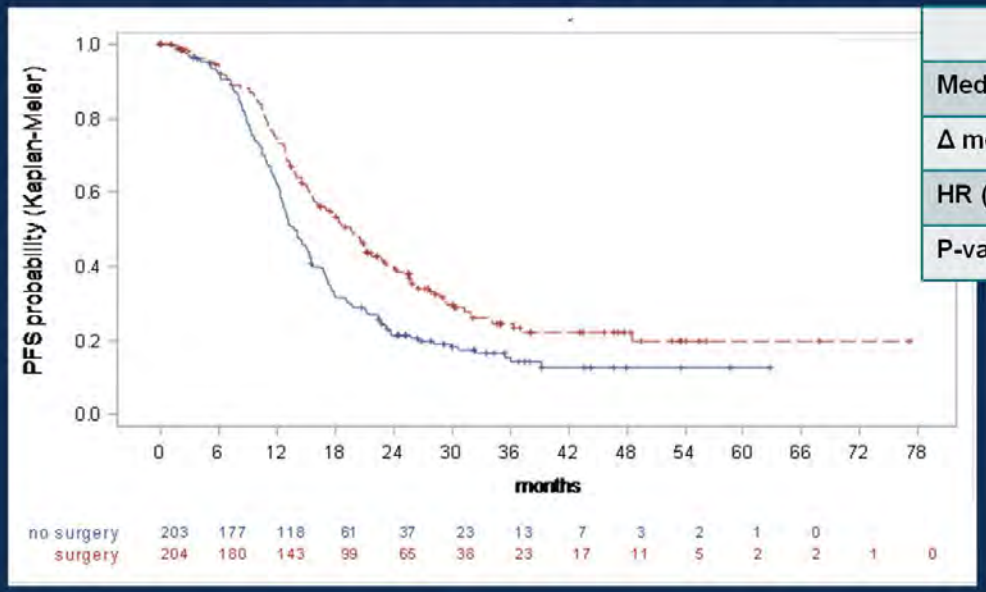
DESKTOP 3 *trial*

AGO DESKTOP III: Outcome 2 (PFS, ITT population)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Surgery	No surgery
Median PFS	19.6 mos	14.0 mos
Δ median PFS	5.6 mos	
HR (95% CI)	0.66 (0.52 – 0.83)	
P-value	< 0.001	

296 (73%) PFS events

A citorredução proporciona vantagem em SLD de quase 6 meses, no Ca de ovário platino sensível recorrente

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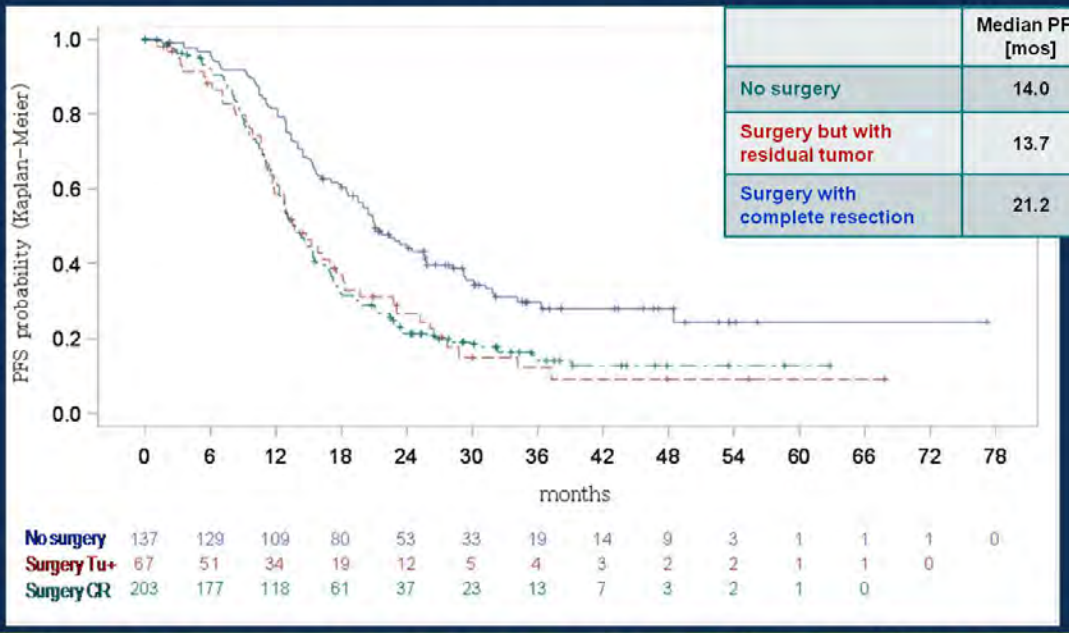
DESKTOP 3 *trial*

AGO DESKTOP III: Outcome 3 (PFS by surgical outcome)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Median PFS [mos]	Δ PFS [mos]	HR (95% CI)	P-value Wald-test
No surgery	14.0	-	1	-
Surgery but with residual tumor	13.7	- 0.3	0.98 (0.71 – 1.35)	0.8952
Surgery with complete resection	21.2	+ 7.2	0.56 (0.43 – 0.72)	< 0.0001

Pacientes com doença residual comportam-se como aqueles que não foram submetidos a cirurgia citorredutora.

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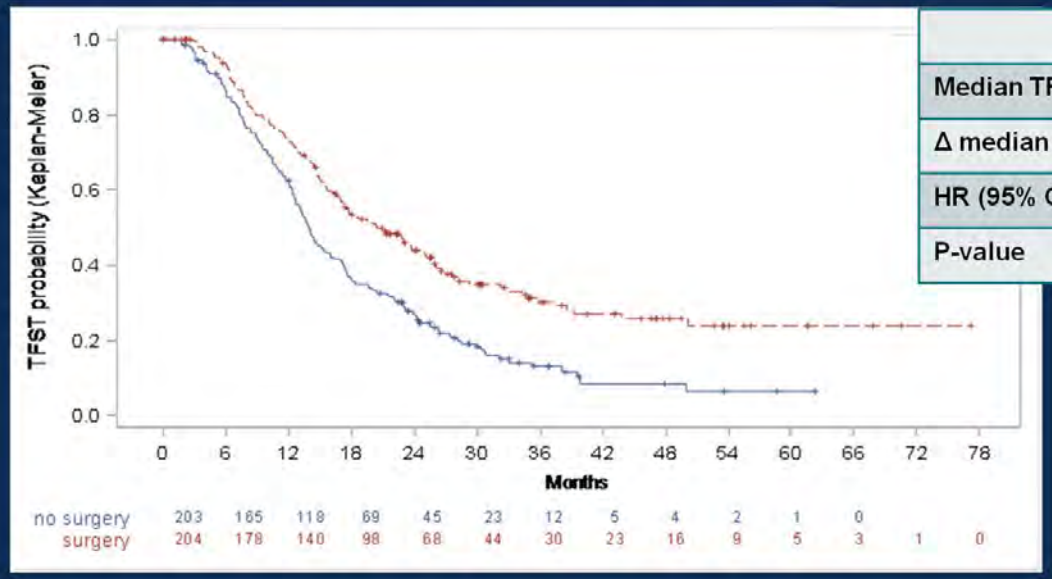
DESKTOP 3 *trial*

AGO DESKTOP III: Outcome 5 (TFST = time to 3rd line)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Surgery	No surgery
Median TFST	21.0 mos	13.9 mos
Δ median TFST	7.1 mos	
HR (95% CI)	0.61 (0.48 – 0.77)	
P-value	< 0.001	

Esses resultados se traduzem em um tempo para 3ª linha de tratamento significativamente maior, no grupo operado.

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DESKTOP 3 *trial*

AGO DESKTOP III: Outcome 2 (Mortality / Morbidity)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	No surgery	Surgery	
30-days mortality (%)	-	-	Peri-OP 1
60-days mortality (%)	1 pt (0.49%)	-	Peri-OP 2
90-days mortality (%)	1 pt (0.49%)	1 pt (0.49%)	Peri-OP $_{MAYO}$
6 months mortality (%)	5 pts (2.46%)	1 pt (0.49%)	End of 2nd line thx
G 3/4 adverse events occurring within 60 days with a frequency of at least 1% (2 pts) in one arm:			
Fatigue	2 (1%)	1 (0.5%)	0.56
GI-Fistula	2 (1%)	2 (1%)	0.99
Ileus	2 (1%)	1 (0.5%)	0.56
Leucopenia / Neutropenia	**10 (5%)**	**2 (1%)**	**p= 0.02**
Neuropathy	2 (1%)	0 (0%)	0.16
Thrombosis / Embolism	2 (1%)	1 (0.5%)	0.56

Exceto por maiores taxas de leucopenia/neutropenia, não houve maior morbimortalidade no grupo operado

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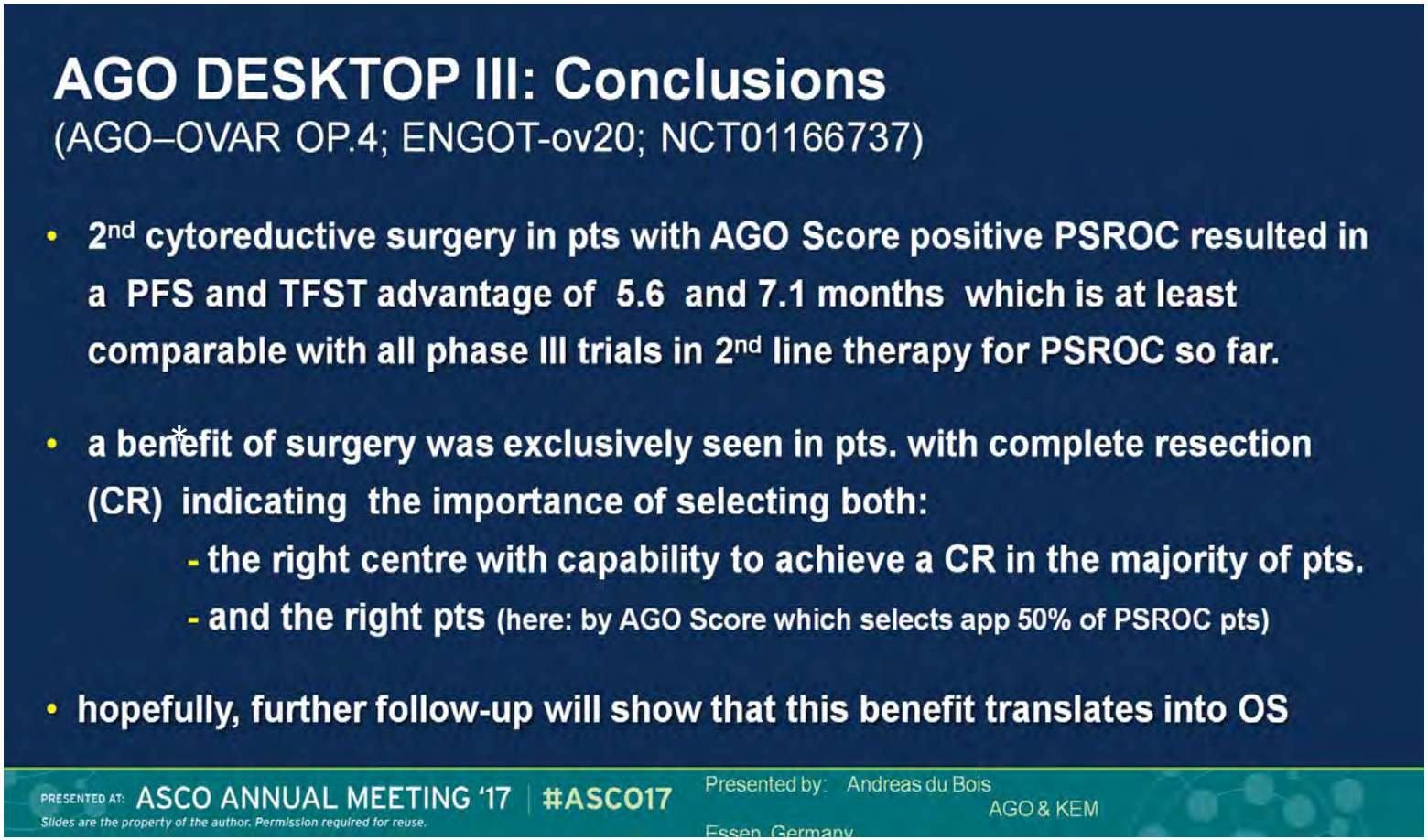
DESKTOP 3 *trial*



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Olaparibe de manutenção: Qual o impacto na Qualidade de vida?

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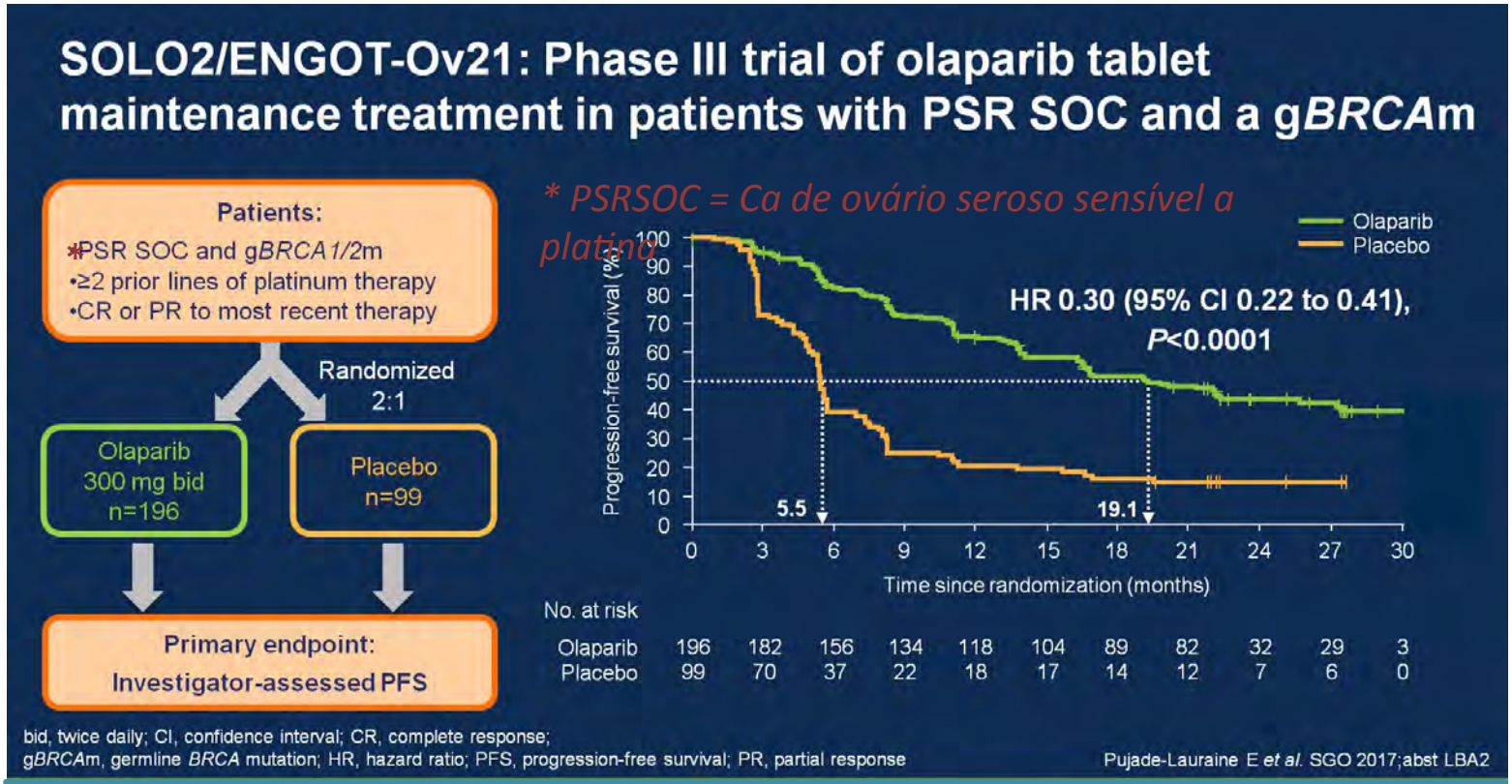
SOLO 2 *trial* (Fase III)



O estudo de fase III SOLO2 demonstrou uma vantagem altamente significante para o uso de Olaparibe de manutenção após resposta a QT

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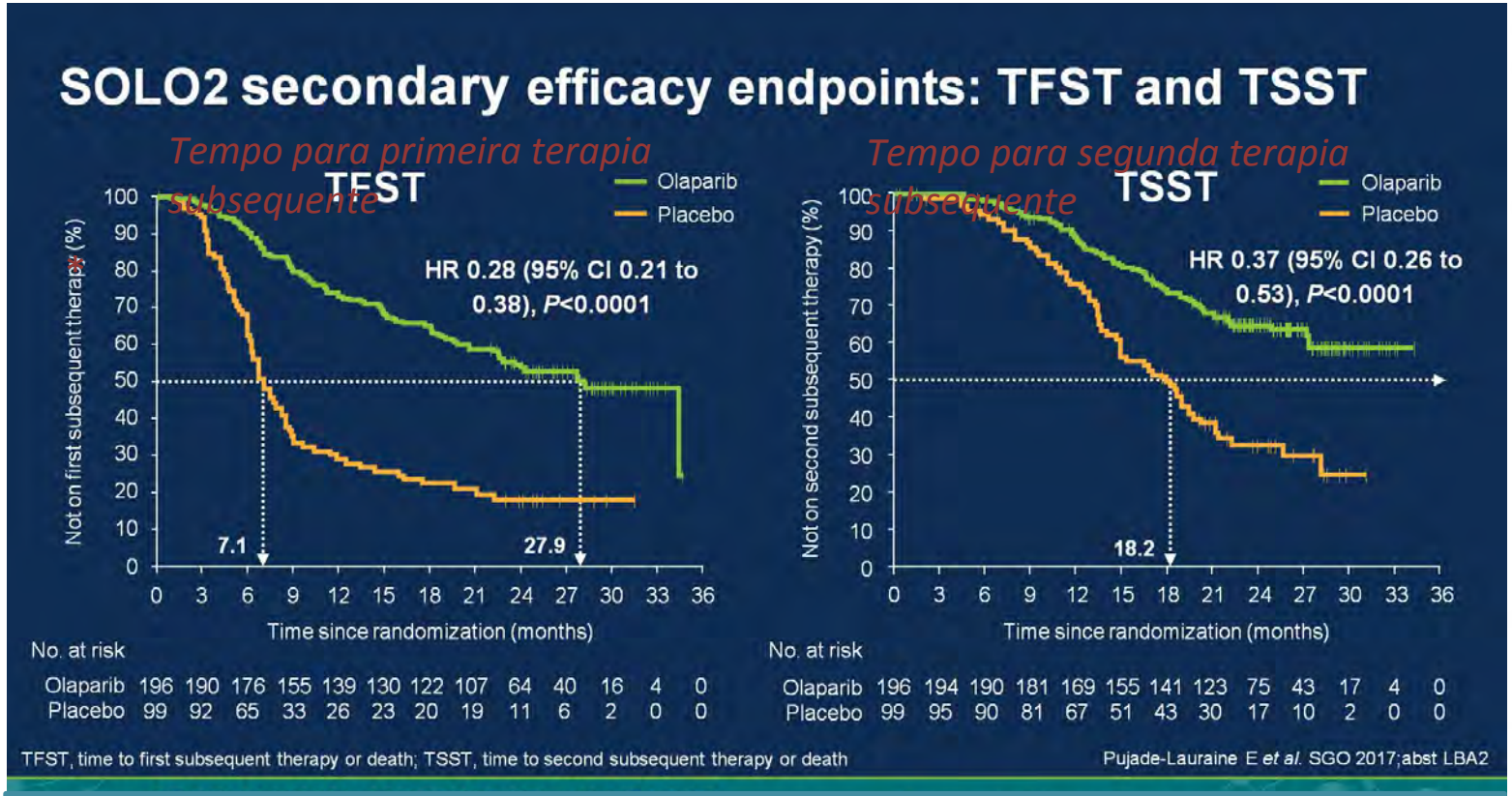
SOLO 2 *trial* (Fase III)



A maior SLP se traduziu também em maiores tempos para 1ª e 2ª terapia subsequentes (estatisticamente significativos)

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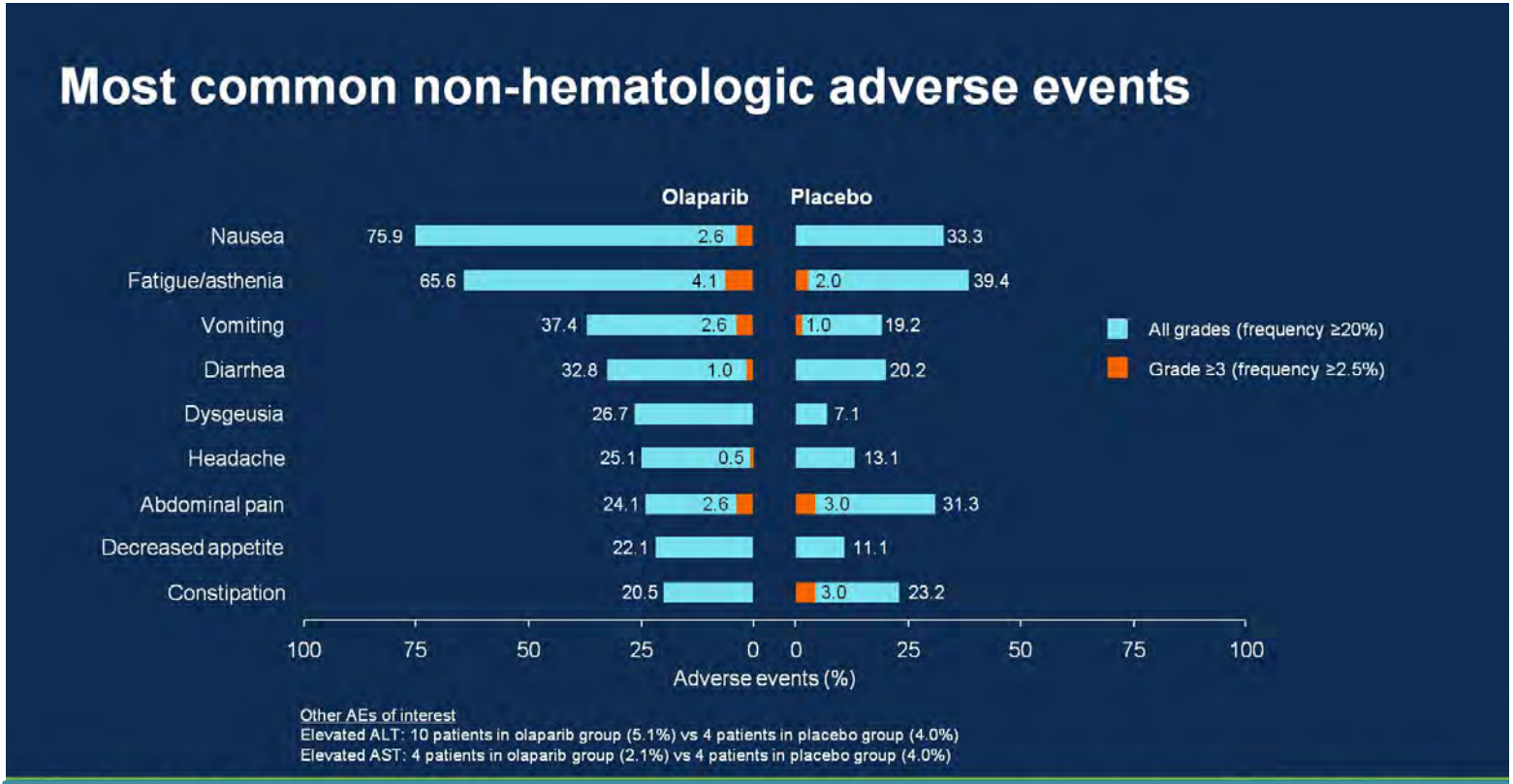
SOLO 2 *trial* (Fase III)



Infelizmente, essa vantagem se dá às custas de maior toxicidade.

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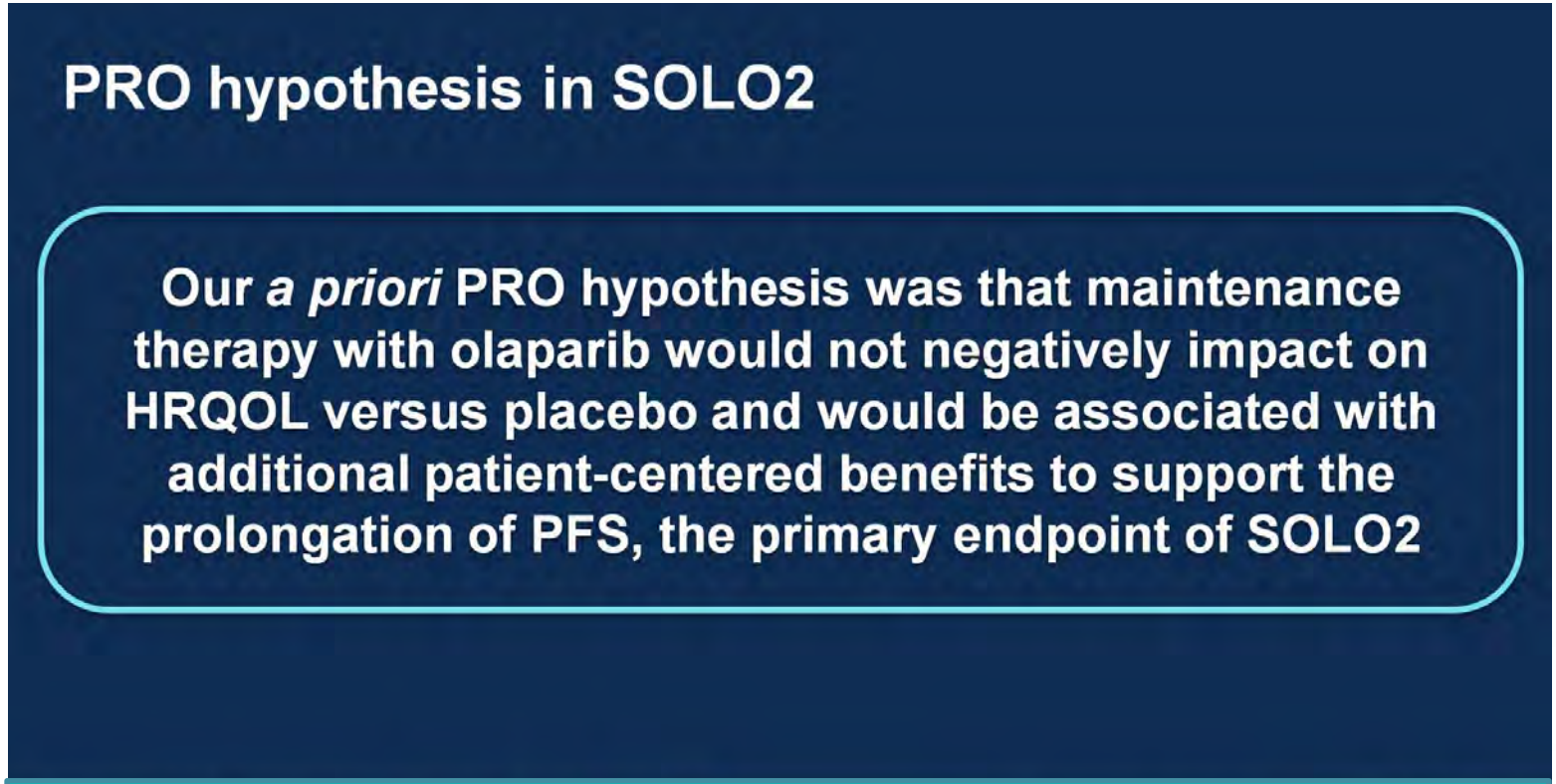
SOLO 2 (fase III): QoL



A proposta dessa análise do SOLO2 é avaliar o impacto na qualidade de vida, causado pelo Olaparibe de manutenção

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SOLO 2 (fase III): QoL

Primary HRQOL endpoint

- Change from baseline in Trial Outcome Index (TOI), an established single targeted index derived from the FACT-O questionnaire
- Includes the most relevant ovarian cancer symptoms, together with functional and physical well-being

A proposta foi avaliar a Qualidade de vida por meio de questionários validados

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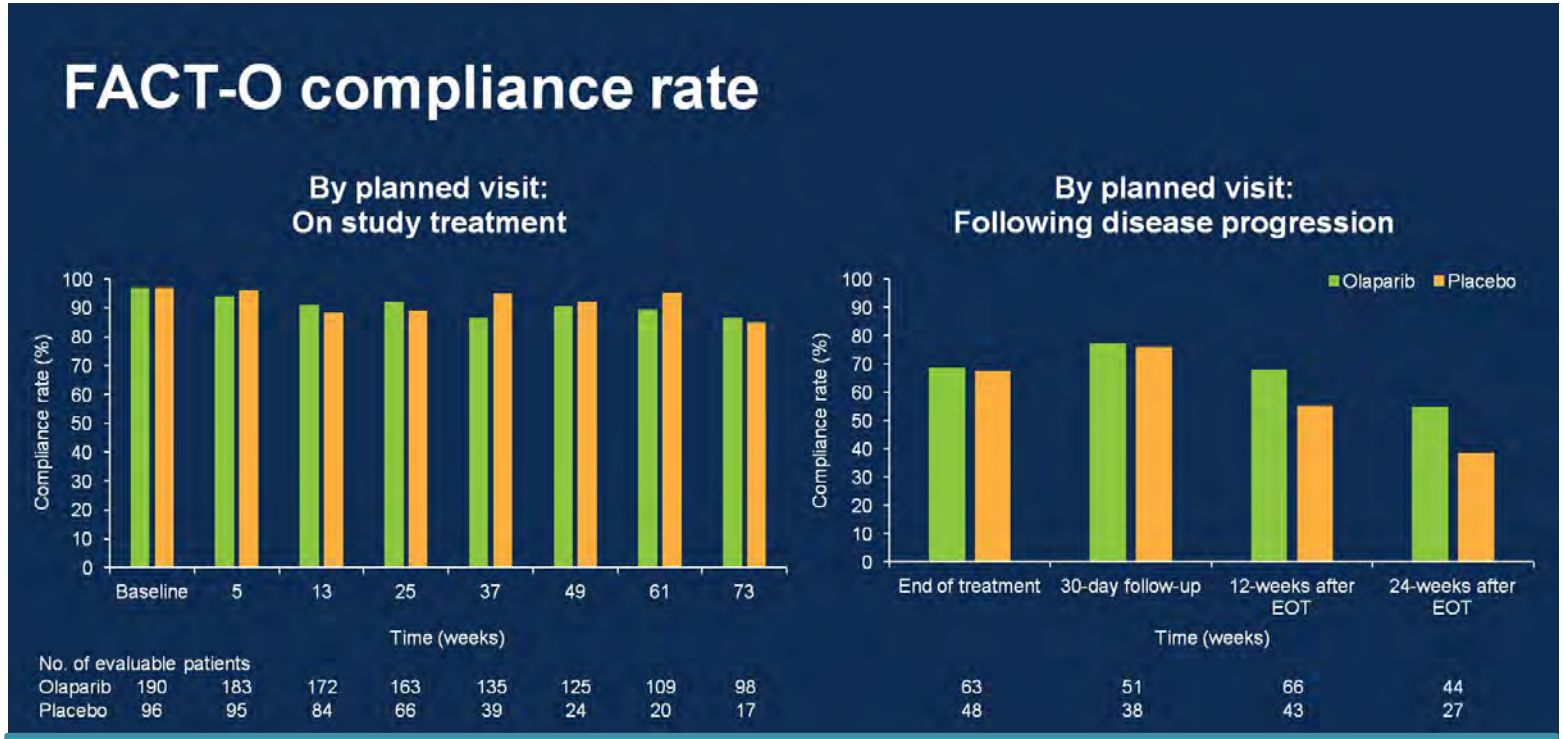
SOLO 2 (fase III): QoL



1) Os questionários eram aplicados na data de inclusão, no D29 e a cada 12 semanas até progressão. Também 30 dias após a última dose e a cada 12 semanas até o cut-off/primeira análise.
2) A adesão ao preenchimento dos dados foi alta até mesmo após progressão.

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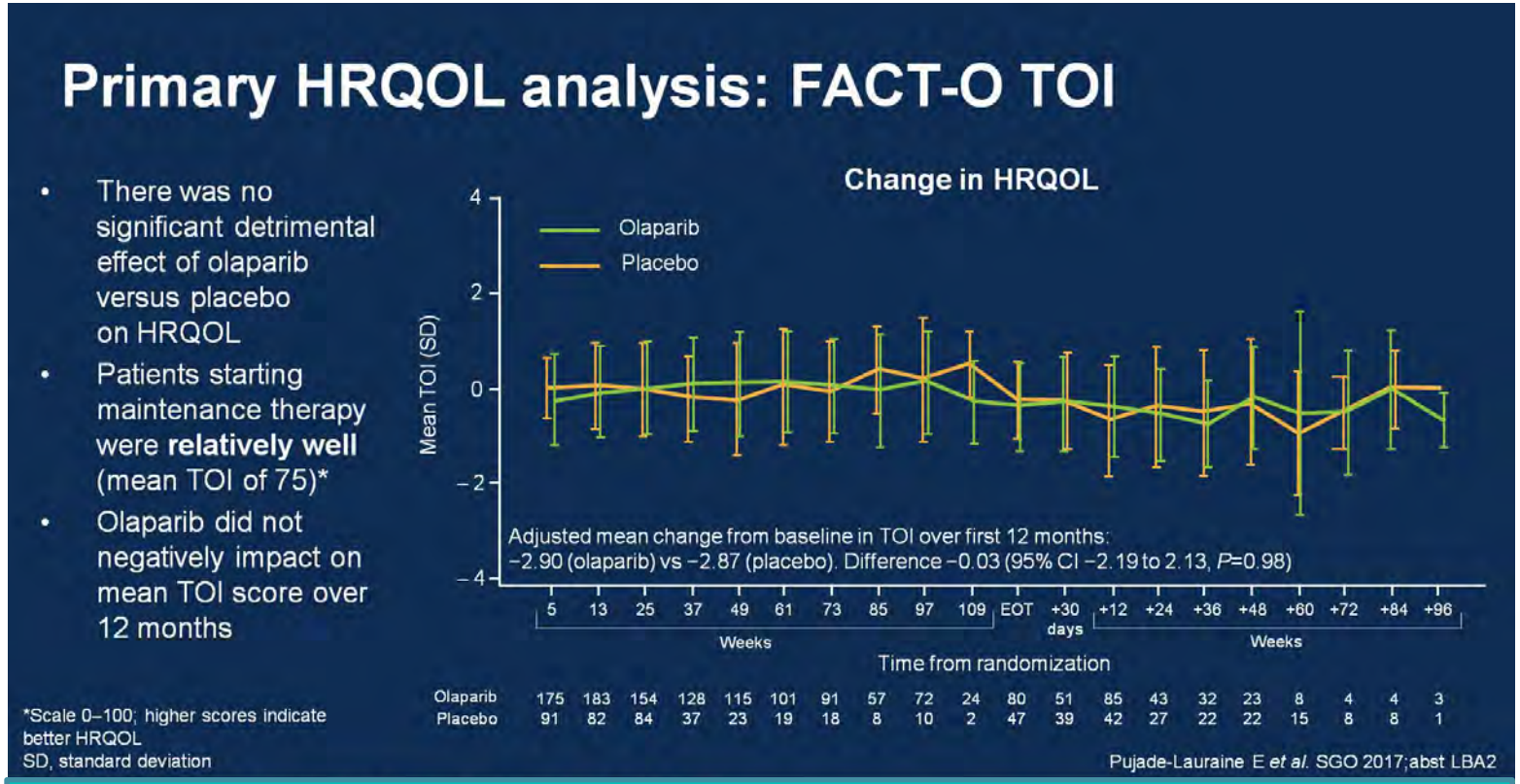
SOLO 2 (fase III): QoL



1) Pelo que se observa na curva, Olaparibe não impactou negativamente no escore médio de Qualidade de vida (HRQOL)

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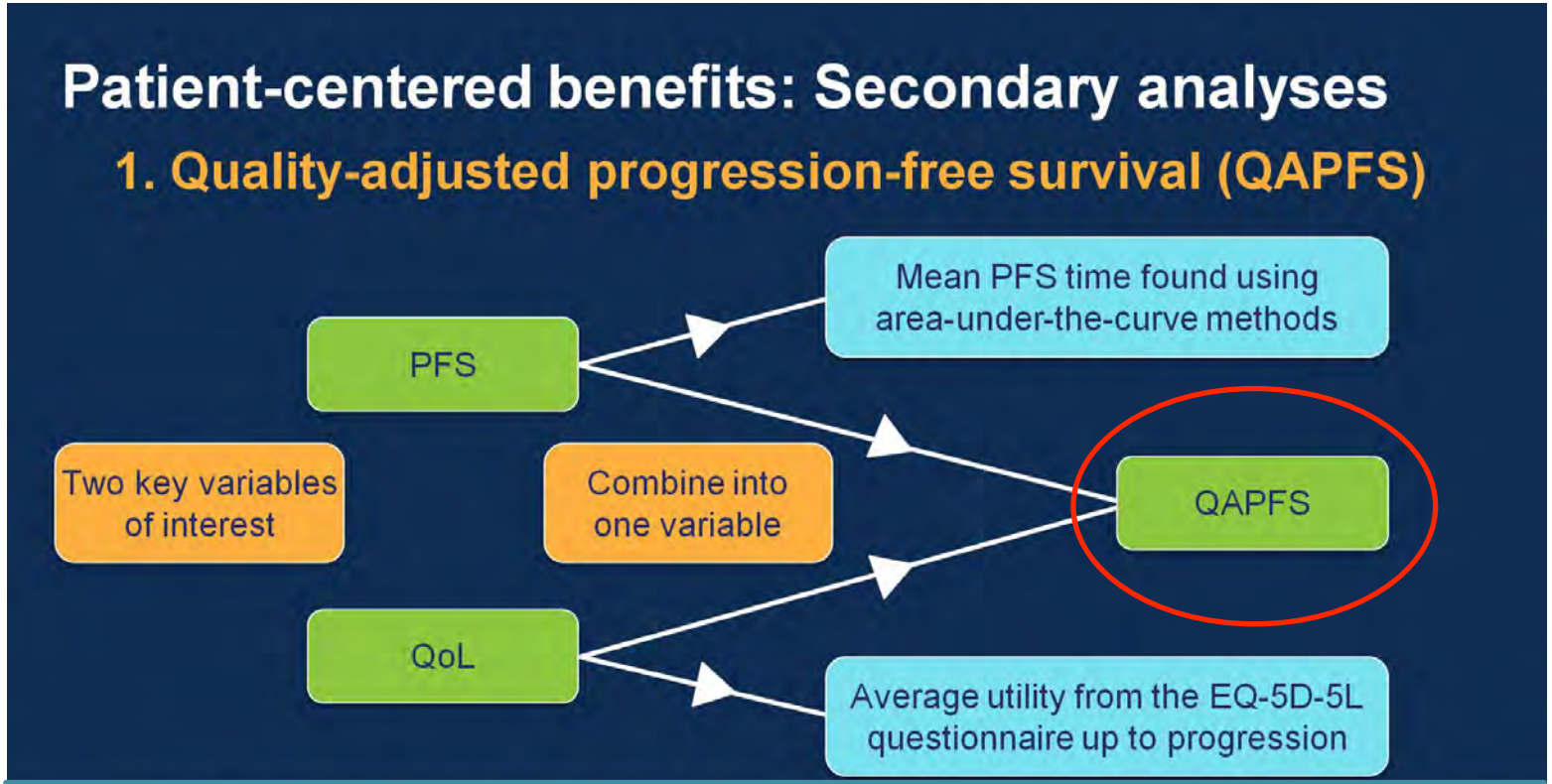
SOLO 2 (fase III): QoL



1) Entretanto, sozinho, esse dado não permite inferir benefício direto aos pacientes.
2) Uma das formas de se tentar melhorar esse dado é fazer uma análise da Qualidade de vida ajustada à sobrevida livre de progressão (QAPFS)

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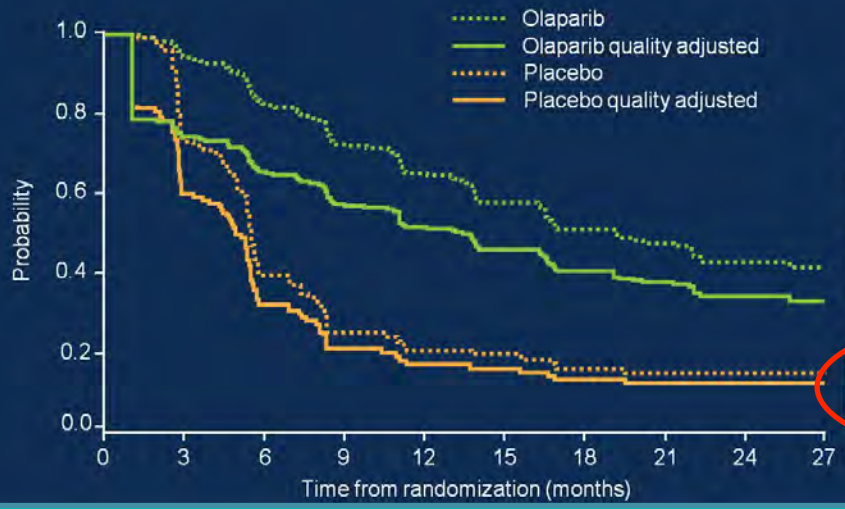
SOLO 2 (fase III): QoL

Results: Quality-adjusted PFS

Significantly longer QAPFS with olaparib versus placebo



	Olaparib (n=185)	Placebo (n=94)	Difference (95% CI)	*P* value
Mean PFS (months)	17.55	8.94	8.61 (6.47 to 10.87)	<0.0001
Mean utility (mixed model)	0.80	0.81	–0.02 (–0.05 to 0.02)	0.284
QAPFS (months)	**13.96**	**7.28**	**6.68 (4.98 to 8.54)**	**<0.0001**

1) Percebe-se que a Qualidade de vida ajustada à sobrevida livre de progressão (QAPFS) é significativamente superior para os usuários de Olaparibe

SOLO 2 (fase III): QoL

Patient-centered benefits: Secondary analyses

2. Time without symptoms of disease or toxicity (TWiST)

- Duration of 'good quality of life' – taking adverse effects into account

- Toxicity – period with significant symptoms post-randomization and before protocol-defined disease progression (or censoring for progression; CTCAE grade ≥2 nausea, vomiting or fatigue)

CTCAE, Common Terminology Criteria for Adverse Events

Outra forma de olhar para esses dados é avaliar o Tempo sem sintomas da doença ou toxicicidade (TWiST). Essa medida leva em consideração a duração da resposta e a influência de náusea, vômito e fadiga na vida do doente.

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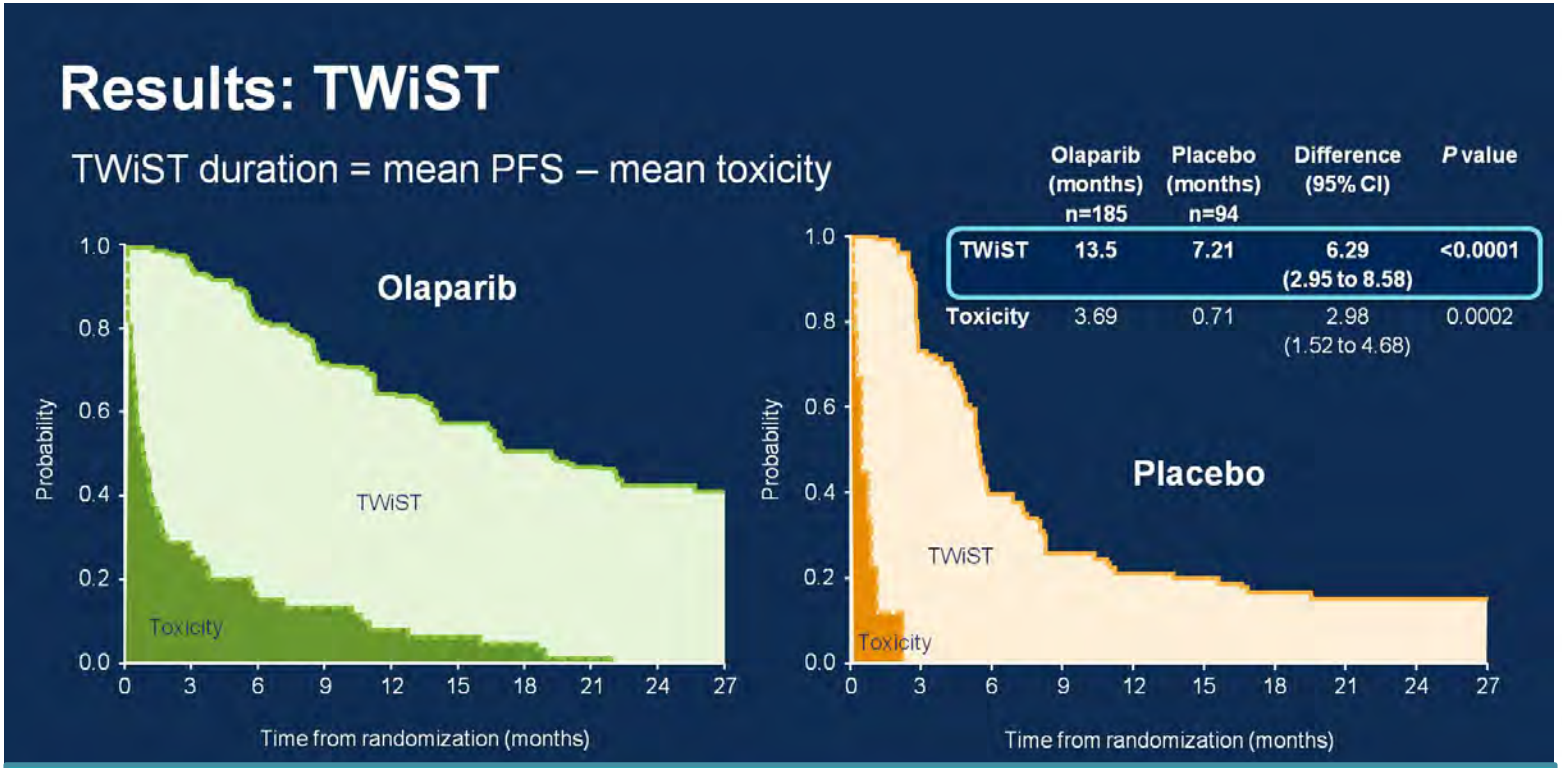
SOLO 2 (fase III): QoL



Pelo gráfico pode-se observar vantagem estatisticamente significativa para o grupo de Olaparibe. A interpretação dessa curva permite inferir que os pacientes que utilizaram o iPARP viveram mais e melhor (com menor influência de eventos adversos).

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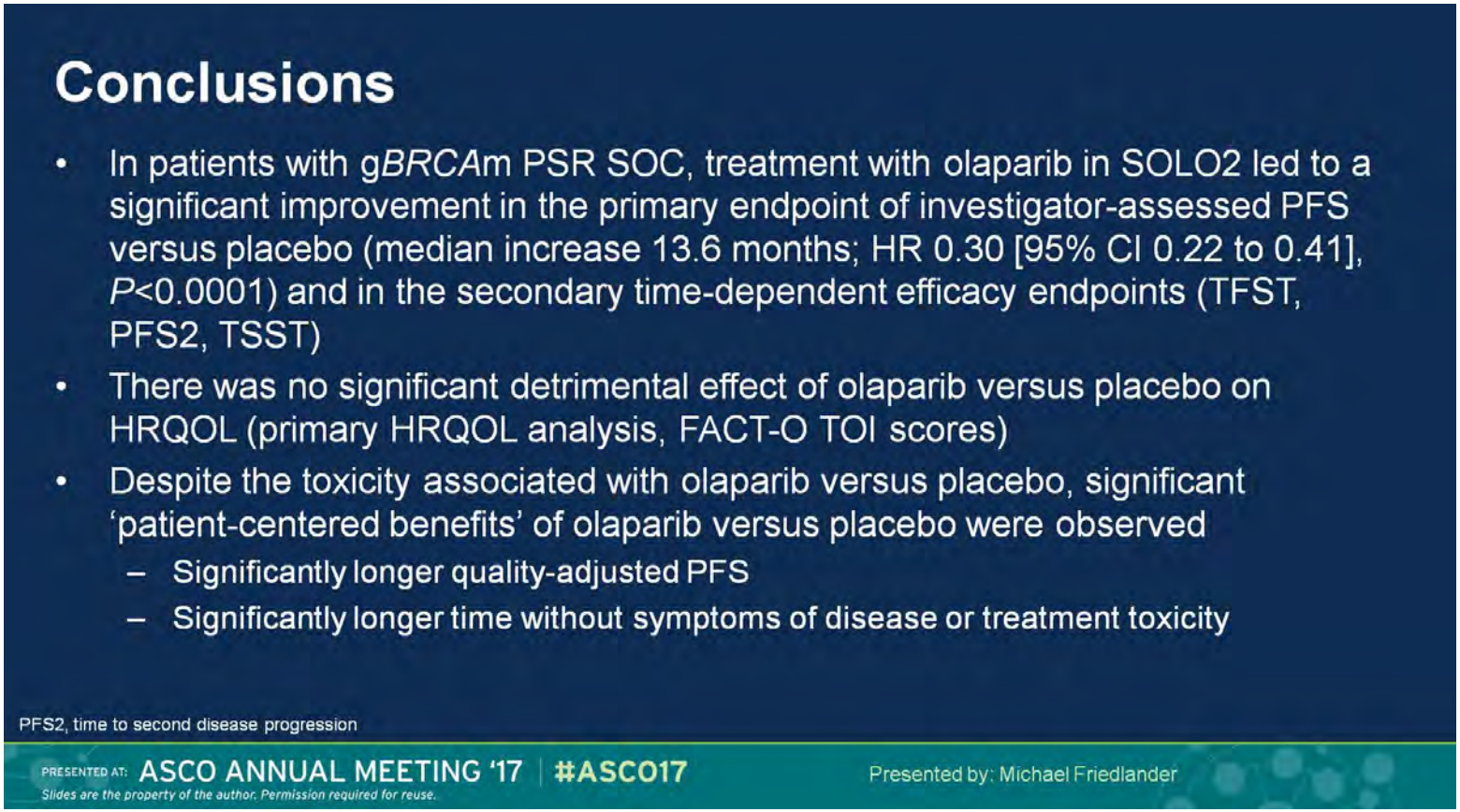
SOLO 2 (fase III): QoL



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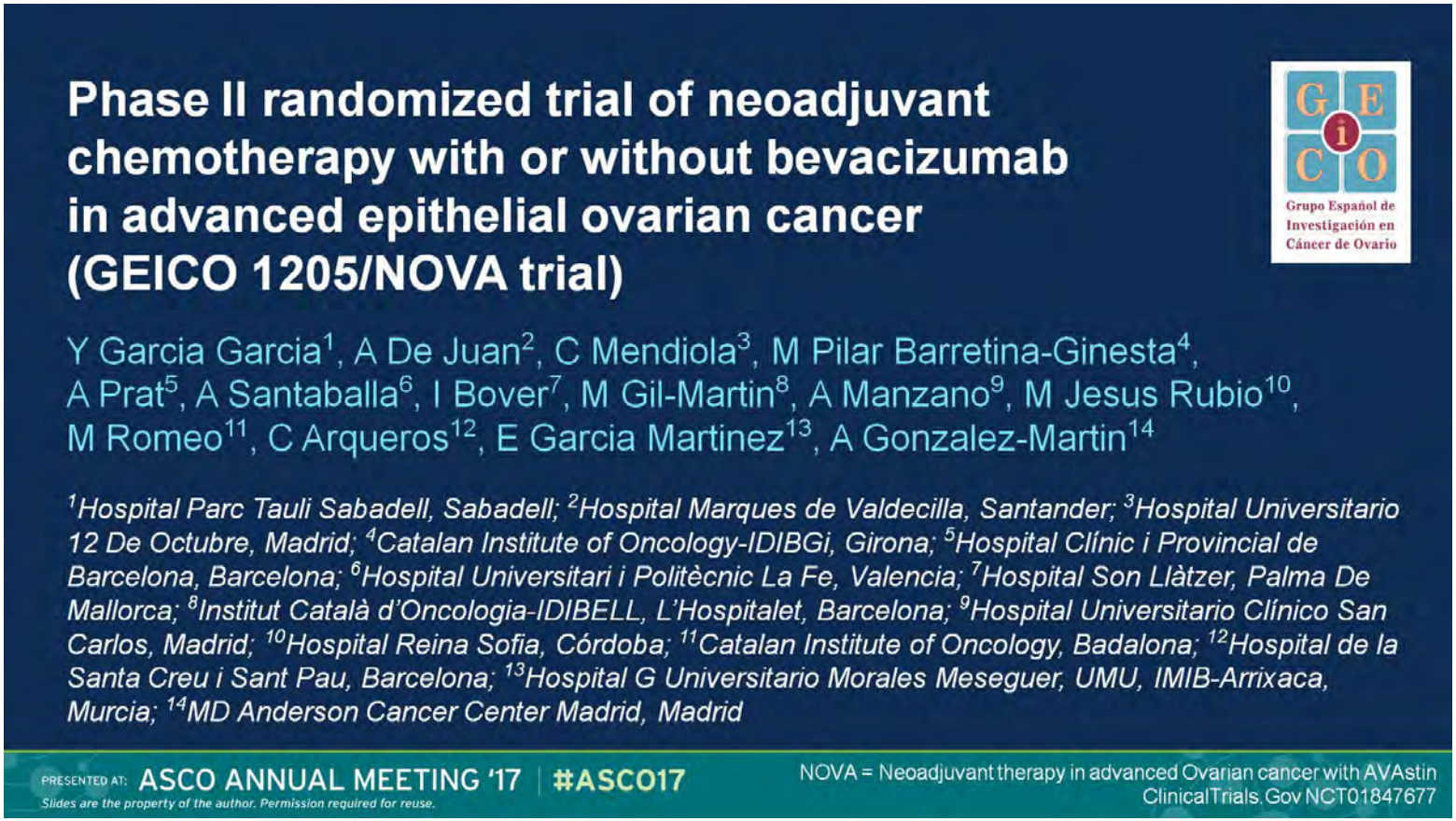
Há papel para Bevacizumabe Neoadjuvante em pacientes que farão cirurgia de intervalo?



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NOVA *trial* (fase II)

Rationale for neoadjuvant BEV

- In advanced eOC, standard therapy is cytoreductive surgery and CP (± BEV)[1]
  - NACT before IDS shows similar efficacy to PDS followed by chemotherapy when the disease is not considered completely resectable, and may improve tolerability[2,3]
- Adding BEV to front-line CP significantly improves PFS[4,5]
  - OS was also improved in patients at high risk of progression[6]
- However, the role of BEV in the neoadjuvant setting is not well defined
- We report the primary analysis from the randomized phase II NOVA trial evaluating neoadjuvant BEV

BEV = bevacizumab; CP = carboplatin + paclitaxel; eOC = epithelial ovarian cancer; IDS = interval debulking surgery; NACT = neoadjuvant chemotherapy; OS = overall survival; PDS = primary debulking surgery; PFS = progression-free survival

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[1]Karam Ann Oncol 2017; [2]Vergote NEJM 2010; [3]Kehoe Lancet 2015; [4]Burger NEJM 2011; [5]Perren NEJM 2011; [6]Oza Lancet Oncol 2015

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NOVA *trial* (fase II)

Well-balanced baseline characteristics

Characteristic		CP alone (n=33)	CP + BEV (n=35)
Median age, years (range)		57 (36–82)	63 (33–78)
ECOG PS, n (%)	0 1 2	5 (15) 21 (64) 7 (21)	8 (23) 24 (69) 3 (9)
Origin of cancer, n (%)	Ovary Primary peritoneal Fallopian tube	25 (76) 7 (21) 1 (3)	31 (89) 4 (11) 0
FIGO stage, n (%)	IIIC IV	22 (67) 11 (33)	23 (66) 12 (34)
Histological subtype, n (%)	Serous Adenocarcinoma Endometrioid/other	26 (79) 5 (15) 2 (6)	27 (77) 7 (20) 1 (3)
Histological grade, n (%)	Grade 3 (poorly differentiated)	32 (97)	35 (100)

Os grupos estavam bem balanceados e eram compostos por mais pacientes Estágio IIIC (66%), seroso (78%) e pobremente diferenciado (G3)

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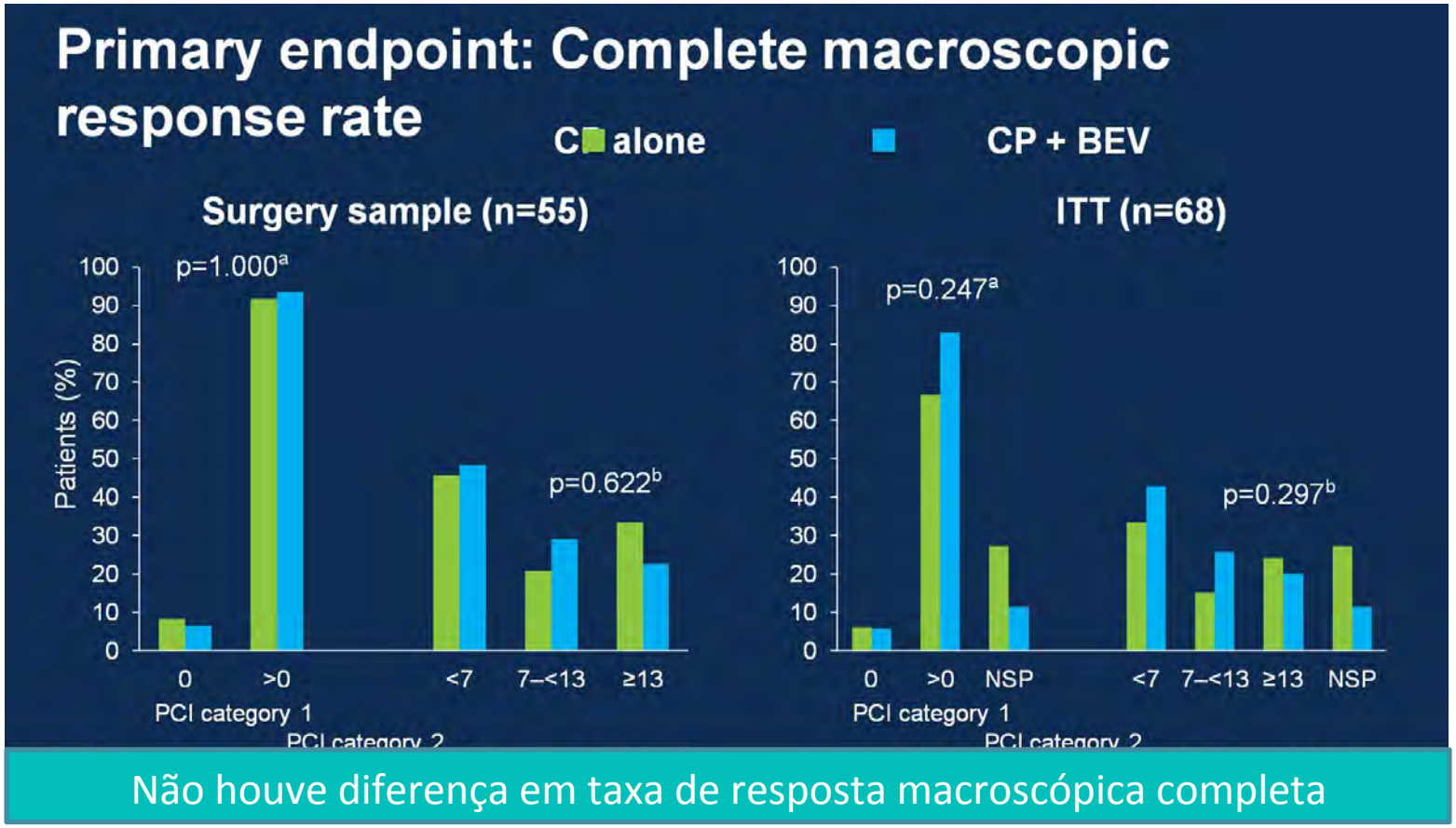
NOVA *trial* (fase II)



Não houve diferença em taxa de resposta macroscópica completa

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NOVA *trial* (fase II)

Secondary endpoints (ITT population)

No. of patients (%)		CP alone (n=33)	CP + BEV (n=35)	p-value
IDS surgical feasibility		22 (67)	31 (89)	0.029[a]
Surgical outcome	Complete resection/optimal surgery	21 (64)	23 (66)	0.858[a]
	Suboptimal	1 (3)	8 (23)	0.028[b]
	Unresectable	2 (6)	0	0.232[b]
	No surgery[c]	9 (27)	4 (11)	0.097[a]
Best response (RECIST)		(n=32) 22 (69)	(n=32) 28 (88)	0.175[a]

- Consistent results in the PP population (n=64)

[a]Chi-squared test. [b]Fisher's exact test
[c]Surgery was planned in 2 patients but they were subsequently considered unresectable. Surgery was not attempted in the remaining patients
RECIST = Response Evaluation Criteria in Solid Tumors

Maior taxa de cirurgia de intervalo para o grupo que usou BEV. Os demais achados foram destituídos de valor estatístico

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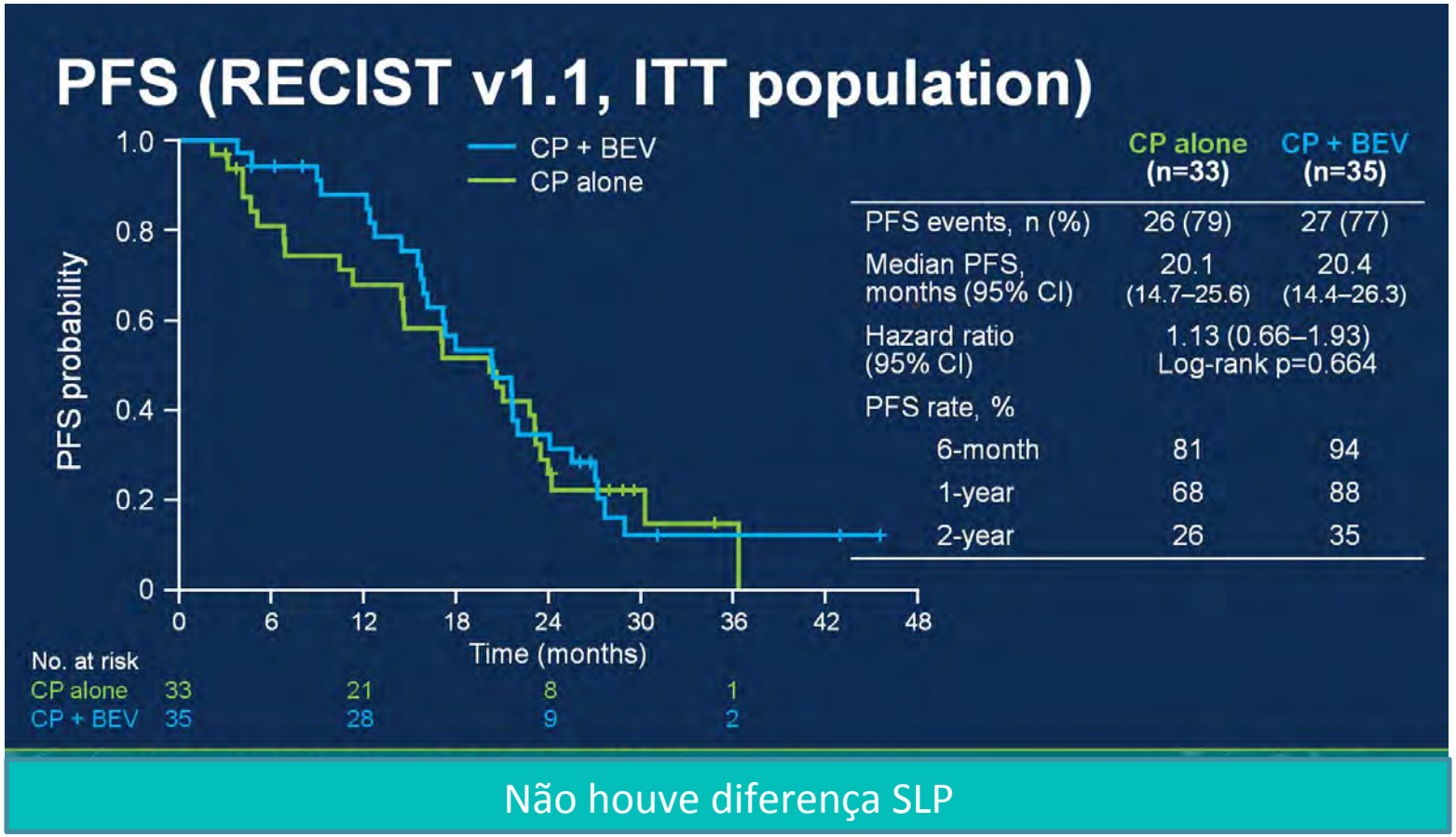
NOVA *trial* (fase II)



Não houve diferença SLP

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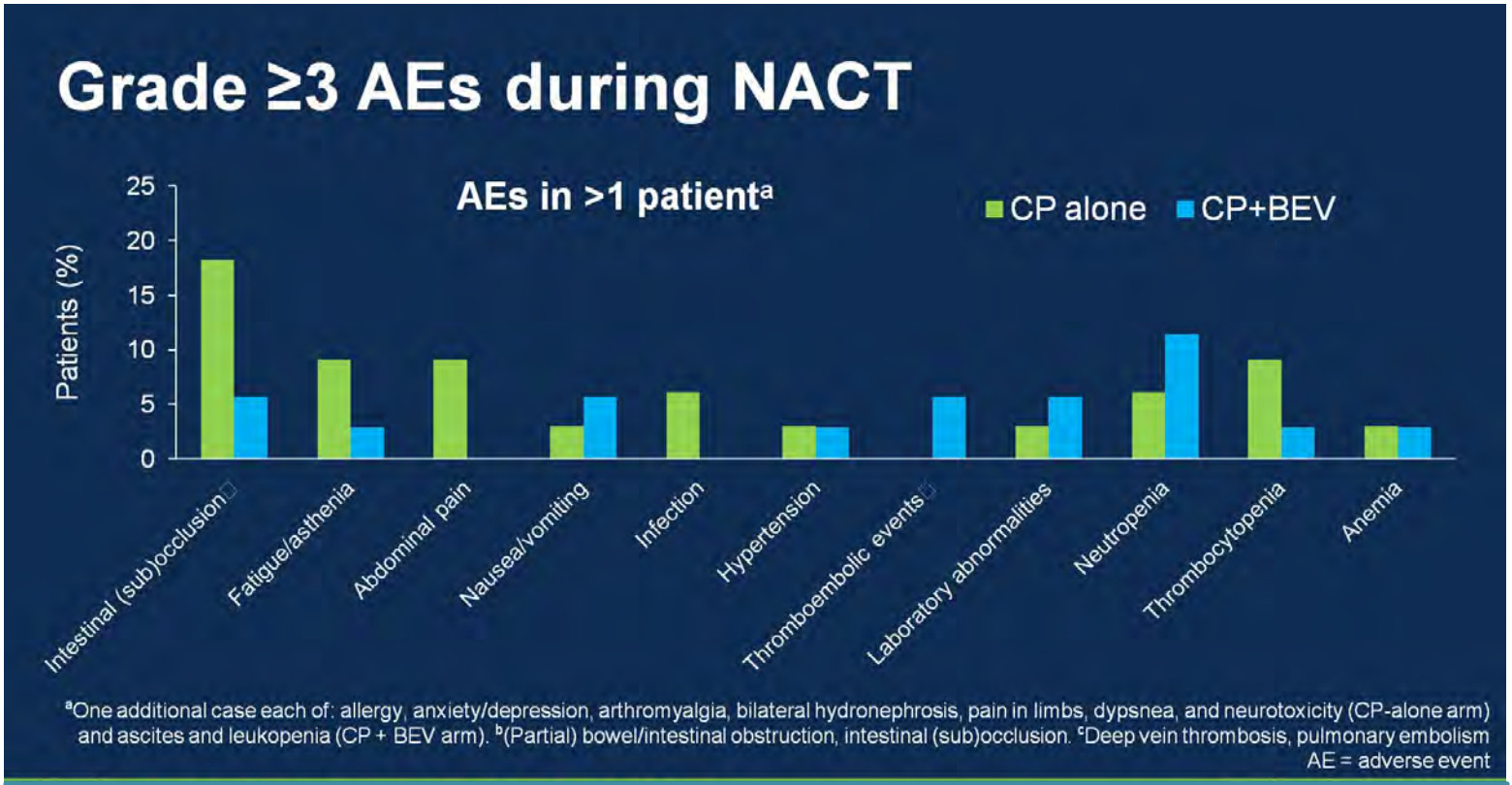
NOVA *trial* (fase II)



Padrão de distribuição de EVENTOS ADVERSOS > G3

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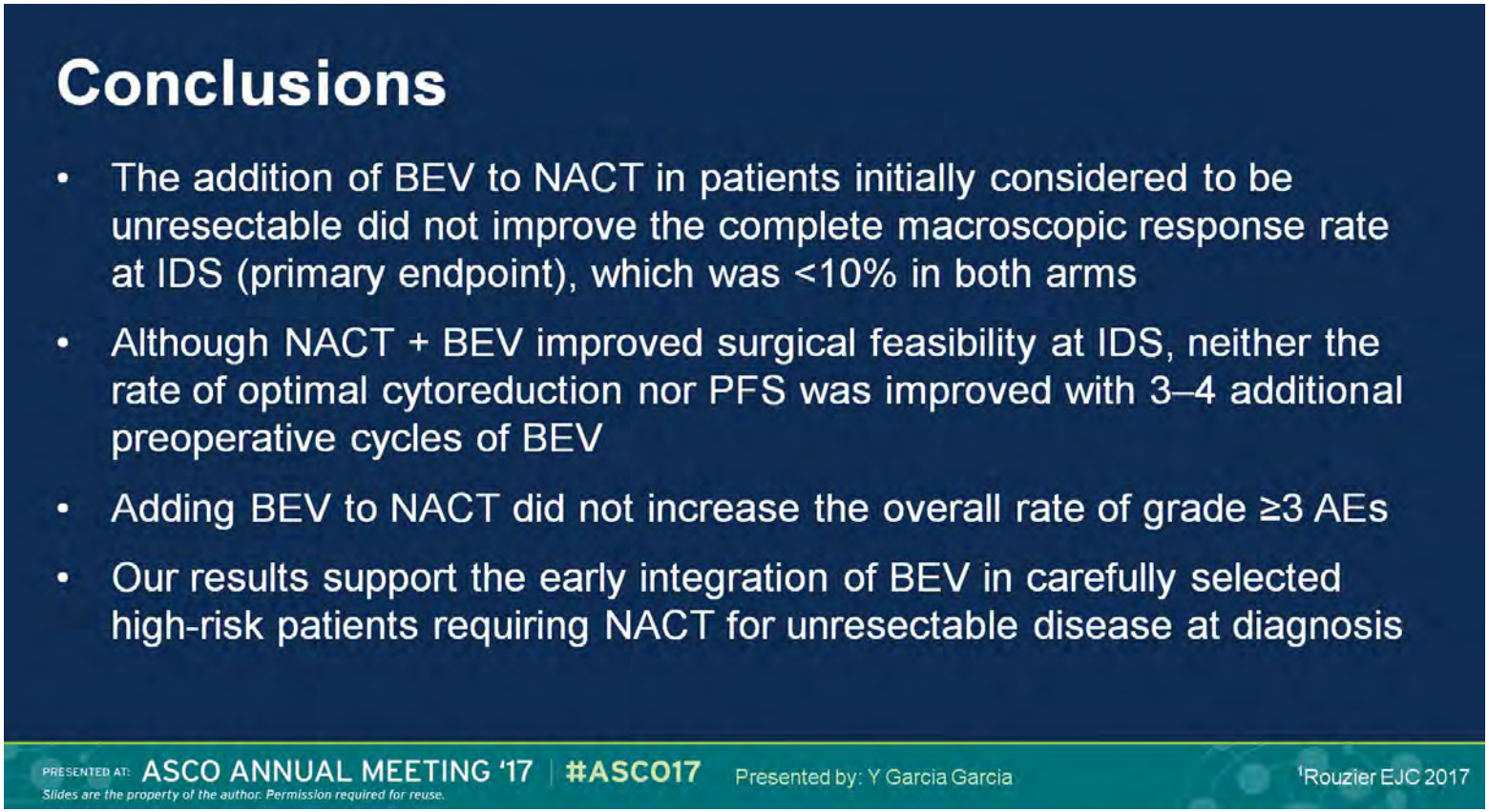
NOVA *trial* (fase II)



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Endométrio

Resultados finais do PORTEC-3

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PORTEC-3

Background of the PORTEC-3 trial

- 15% of endometrial cancers have high-risk features
- Trials of chemotherapy (CT) alone vs radiation therapy (RT) alone found no differences in PFS or OS

- RTOG phase II CT/RT schedule promising
- NSGO/EORTC phase III trial suggested progression-free survival benefit with sequential RT and CT

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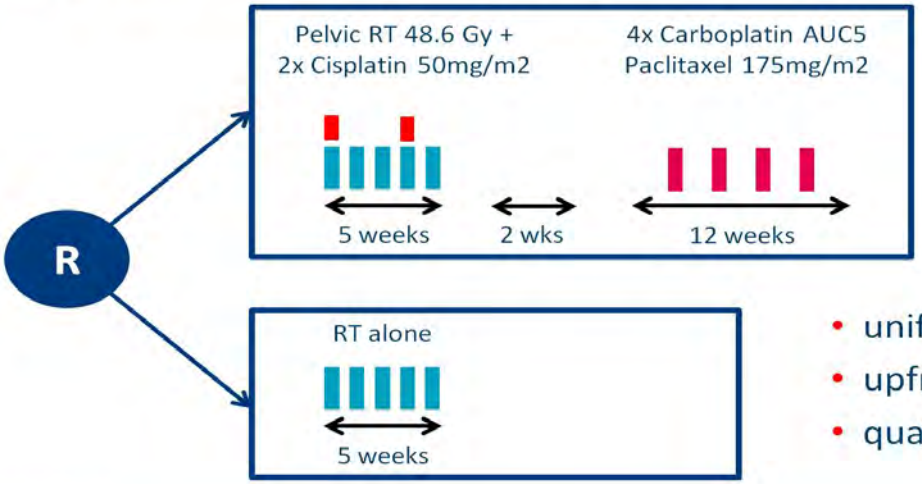
PORTEC-3

PORTEC-3 trial design

- High risk Endometrial Cancer (HREC)



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

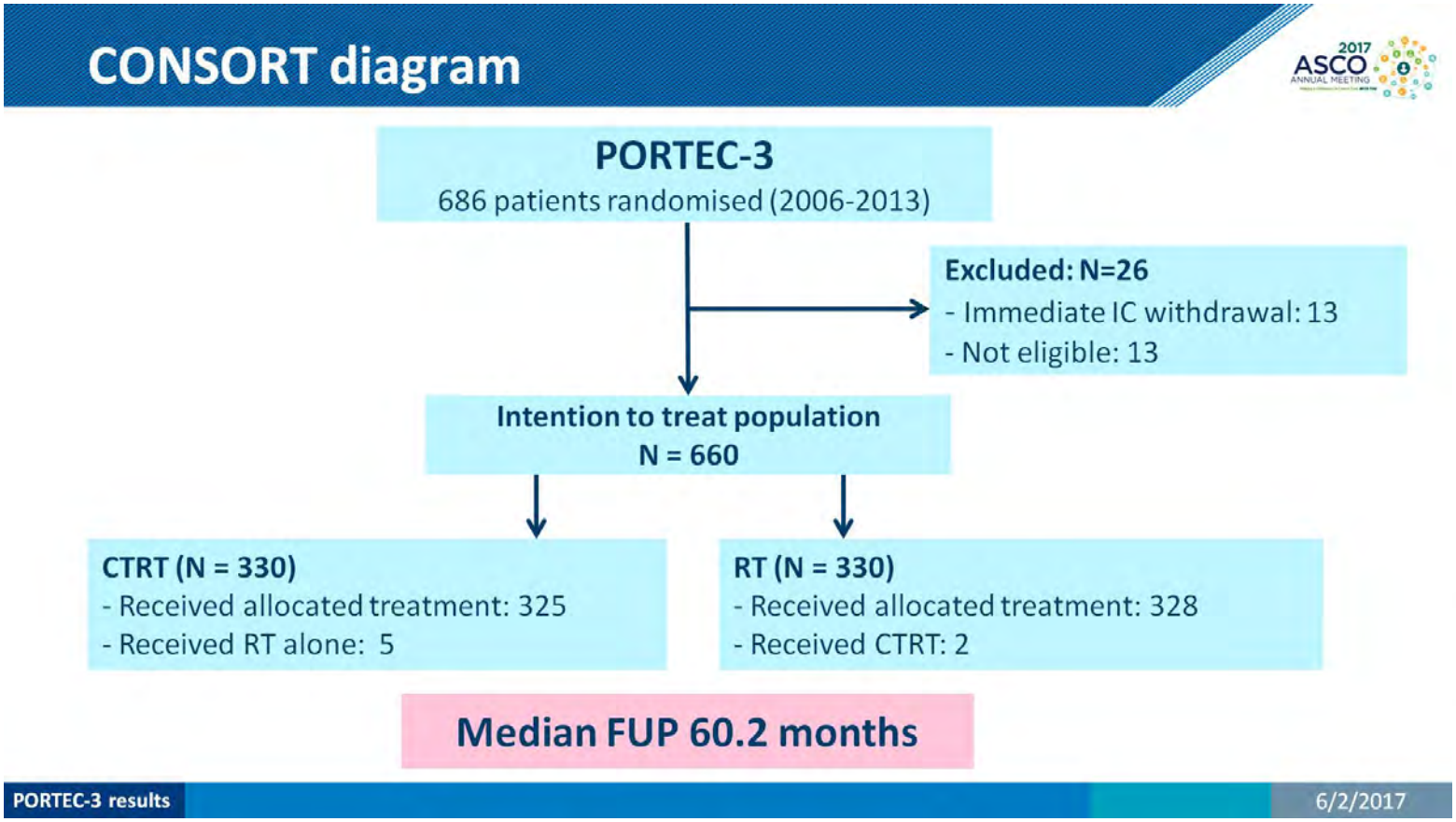
Inclusion criteria

- Endometrial carcinoma
  - stage I grade 3, with deep invasion or LVSI+
  - stage II - III
  - stage I-III serous or clear cell cancers (>25%)
- WHO PS 0-2
- No residual macroscopic tumor after surgery
- Pathology review before randomisation

Endpoints

- Primary endpoints:
  - 5 yr overall survival (OS)
  - 5 yr failure free survival (FFS)
    - FFS: relapse or endometrial cancer-related death
- Secondary endpoints:
  - Vaginal, pelvic and distant recurrence
  - Toxicity and quality of life

PORTEC-3



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PORTEC-3

Patient characteristics

Patient characteristics	RT alone	CTRT
Age (yr)		
Median	62.0	62.4
IQ Range	55.8-68.2	56.5-67.9
WHO PS (%)		
0-1	98.5%	98.5%
2	1.5%	1.5%
Comorbidities (%)		
Diabetes	10.9%	13.7%
Hypertension	31.6%	35.2%
Cardiovascular	6.1%	8.9%

Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

30% I e 25% II

PORTEC-3 results 6/2/2017

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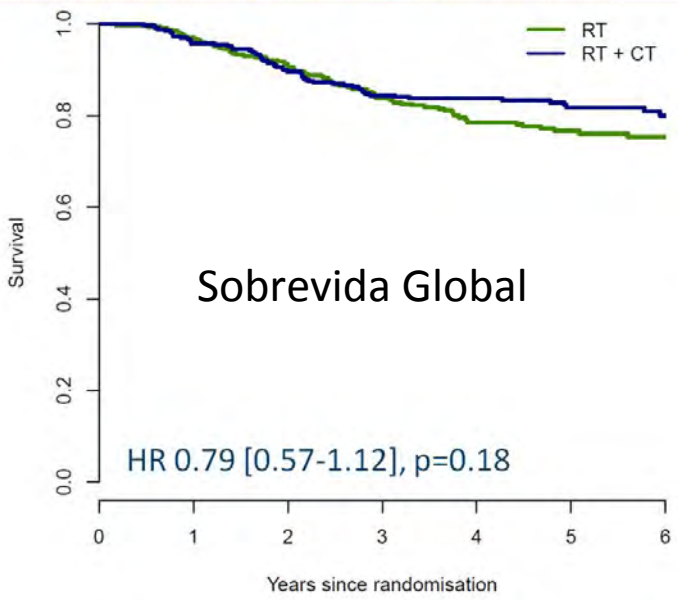
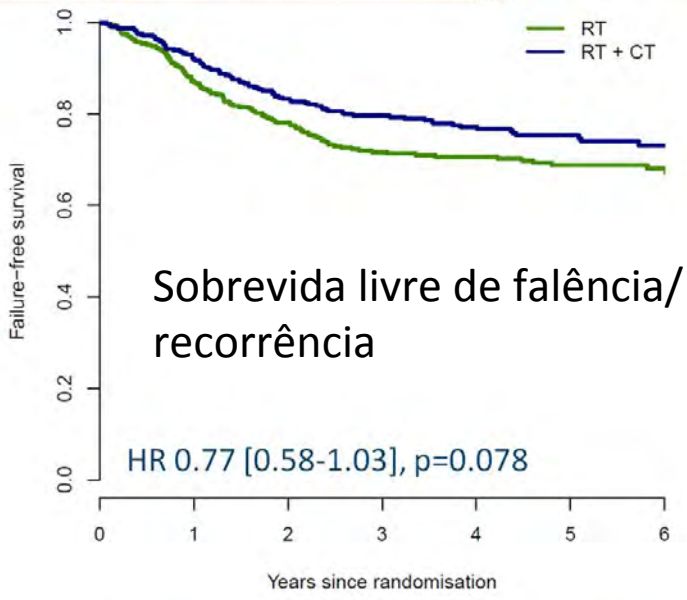
PORTEC-3

Survival (OS and FFS)



Sobrevida Global

5 yr OS: 82% (CTRT) versus 77% (RT)



Sobrevida livre de falência/ recorrência

5 yr FFS: 76% (CTRT) versus 69% (RT)

O estudo falhou em comprovar seus 2 endpoints primários

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First sites of recurrence

5 years	CTRT		RT		HR	P-value
	N	%	N	%		
Vaginal recurrence	1	0.30%	1	0.30%	1	1
Pelvic recurrence	3	0.95%	5	1.5%	0.60	0.478
Distant recurrence	76	22.4%	93	28.3%	0.78	0.108
- Distant + vaginal	4	1.2%	4	1.2%		
- Distant + pelvic	11	3.2%	20	6.1%	-	-
- Distant only	61	18.0%	69	21.0%	-	-

Numericamente mais recorrências à distância no grupo só de RT, porém sem significância estatística

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Survival results per stage

Patients with stage III EC:

- Lower 5-year FFS and OS:
  - FFS: 64% stage III versus 79% for stage I-II (p<0.001)
  - OS: 74% vs 83% (p=0.003)
- Greatest benefit of CTRT
  - 5-year FFS 69% for CTRT vs 58% for RT
    [HR 0.66, 95% CI 0.45-0.97, **p=0.032**]
  - 5-year OS 79% vs 70%
    [HR 0.69, 0.44-1.09, p=0.114]

Analisando apenas o subgrupo com Estágio Clínico III, observa-se vantagem tanto em TTF quanto em SG (apenas 40% dos incluídos)

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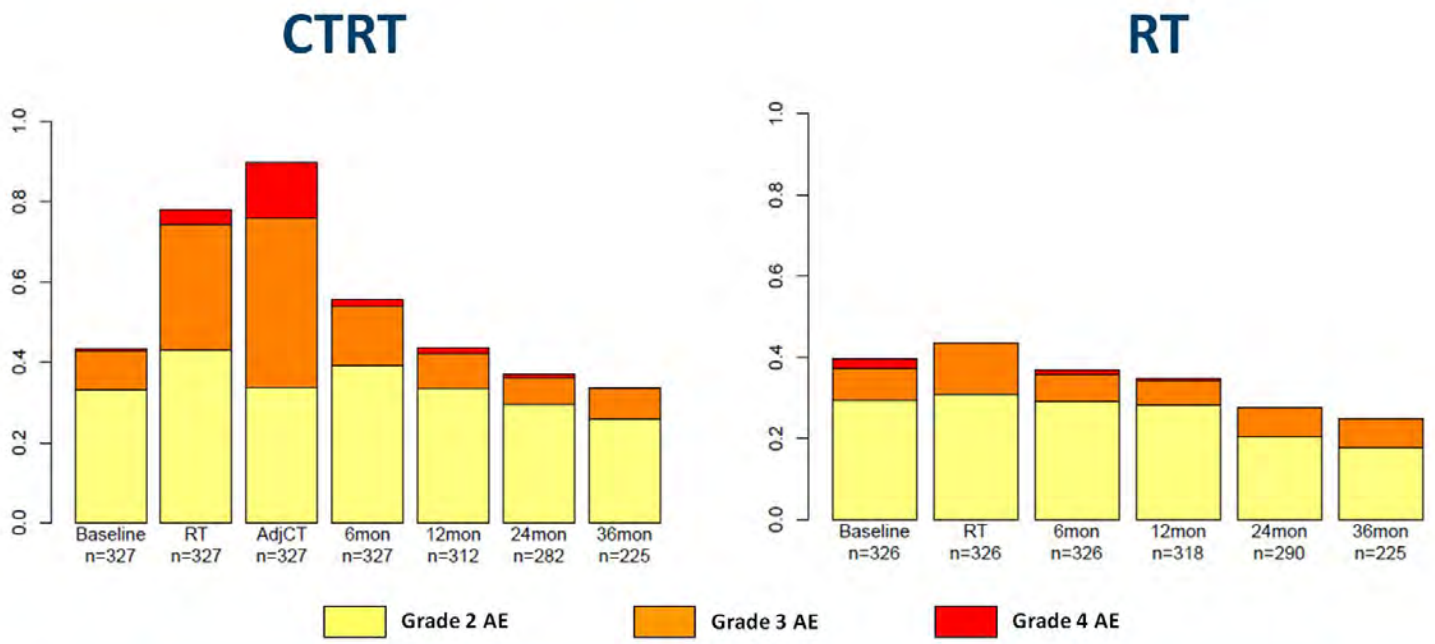
PORTEC-3

Adverse events (CTCAE v3.0)



Como era de se esperar, o grupo da combinação de QT/RT apresentou maiores taxas de eventos adversos G3 e 4

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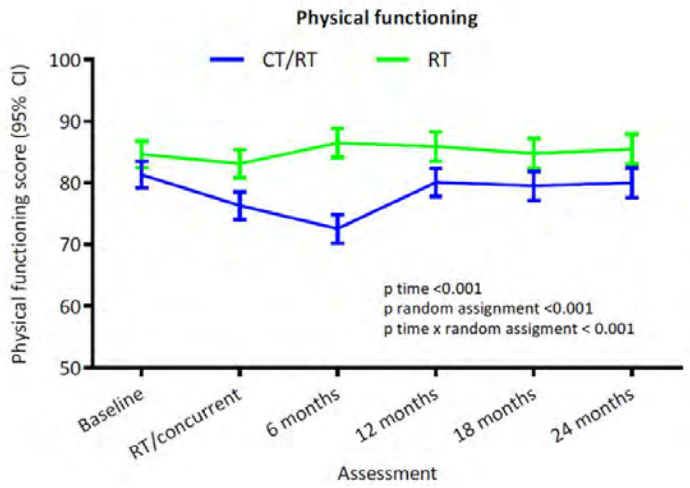
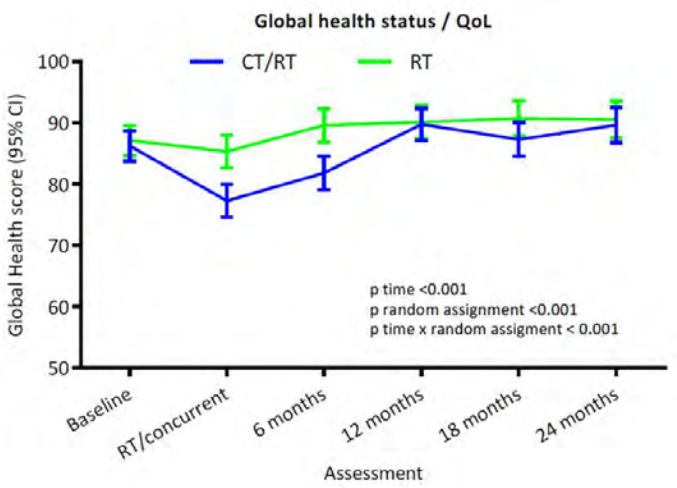
PORTEC-3

Quality of life





A qualidade de vida foi melhor para o grupo que realizou apenas RT. Os resultados foram especialmente piores para o braço QT+RT nos 12 primeiros meses.

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PORTEC-3

Conclusions

CTRT vs RT for high-risk endometrial cancer:

- Trend for improved 5-year FFS
  - Risk reduction of 7% (FFS) and 5% (OS)
- Significant 11% FFS benefit with CTRT for stage III disease
- Significantly more toxicity with CTRT in the first 12 months
- OS analysis may need longer follow-up

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QT/RT versus apenas QT em Câncer de endométrio localmente avançado otimamente operado

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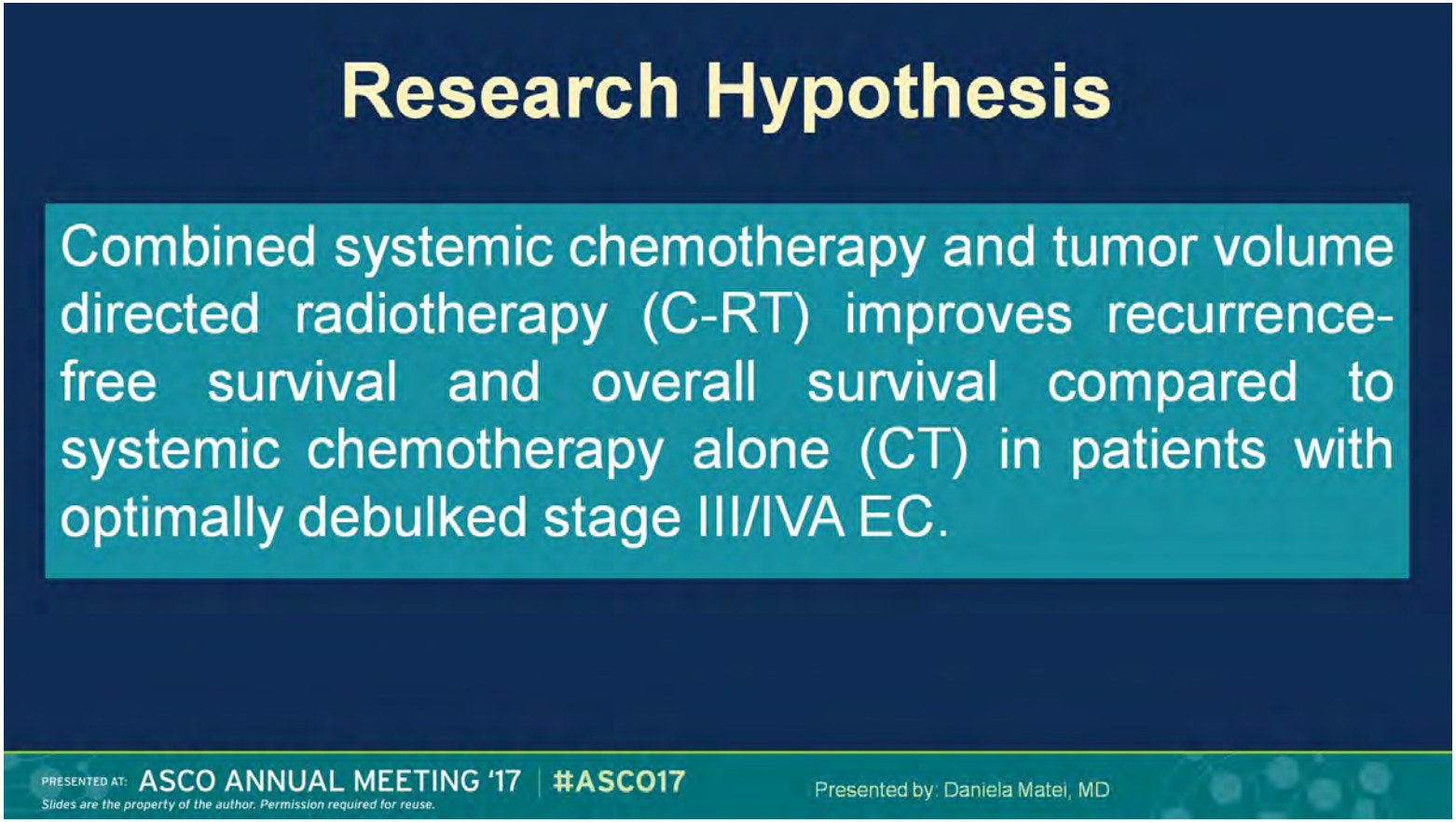
GOG 258



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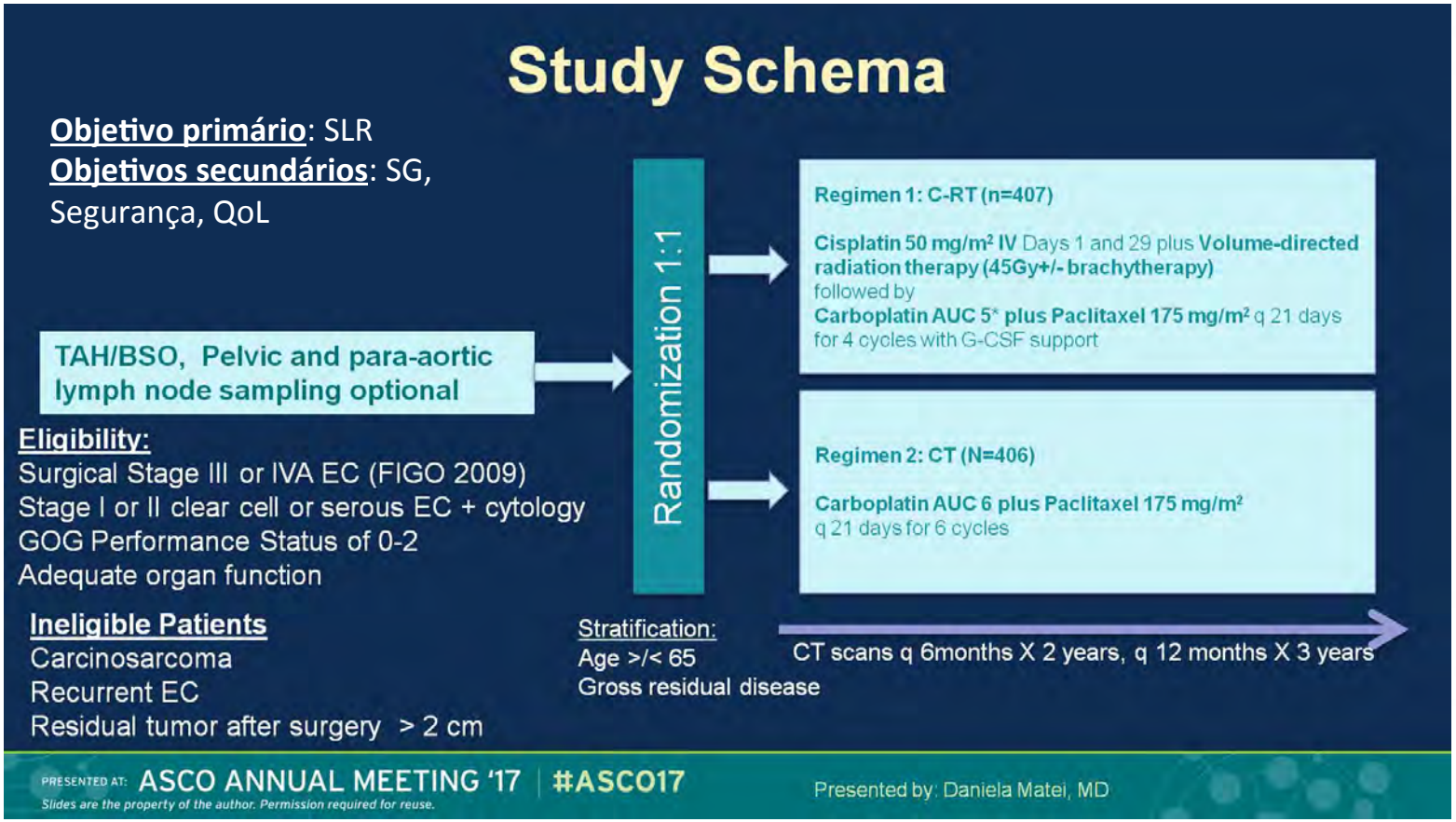

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GOG 258

Patient Characteristics

Characteristic	C-RT (N=370) N	C-RT (N=370) %	CT (N=366) N	CT (N=366) %
Age (mean, range)	60.5	(31-88)	60	(31-85)
Race				
White	291	78.6	279	76.2
Black/African American	37	10.0	42	11.5
Asian/other/not specified	42	11.3	45	12.2
Performance Status				
0	278	75.1	268	73.2
1	88	23.8	96	26.2
2	4	1.1	2	0.5
FIGO Stage (2009)				
Stage 1 or 2	6	1.6	11	3.0
Stage 3A	69	18.6	78	21.3
Stage 3B	15	4.1	13	3.6
Stage 3C	277	74.9	261	71.3
Stage 4A	3	0.8	3	0.8
Histology/Grade				
Endometrioid, grade 1	87	23.5	79	21.6
Endometrioid, grade 2	103	27.8	118	32.2
Endometrioid, grade 3	64	17.3	61	16.7
Serous	66	17.8	65	17.8
Clear Cell	10	2.7	12	3.3
Mixed Epithelial/Other	40	7.7	30	6.3
BMI Category				
Median (range)	32.9	(11.2-65.3)	32.9	(18-60.2)
Normal or underweight	72	19.5	71	19.4
Overweight	84	22.7	81	22.1
Obese Class I-III	214	57.8	214	58.4

Os pacientes incluídos eram de estágios mais avançados (70% IIIC) e cerca de 20% tinham histologia desfavorável

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GOG 258

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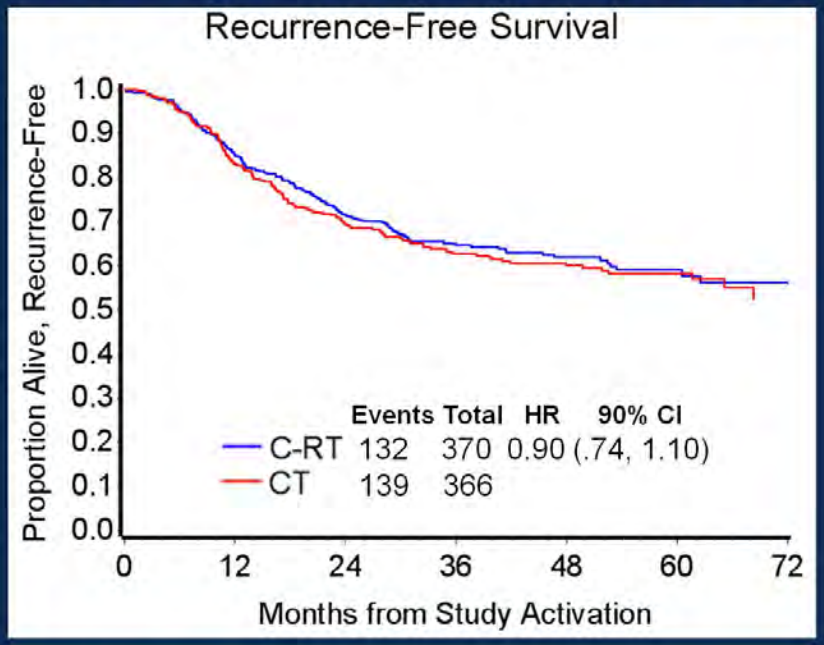
GOG 258

Recurrence-Free Survival



O estudo falhou em comprovar seu Objetivo primário.

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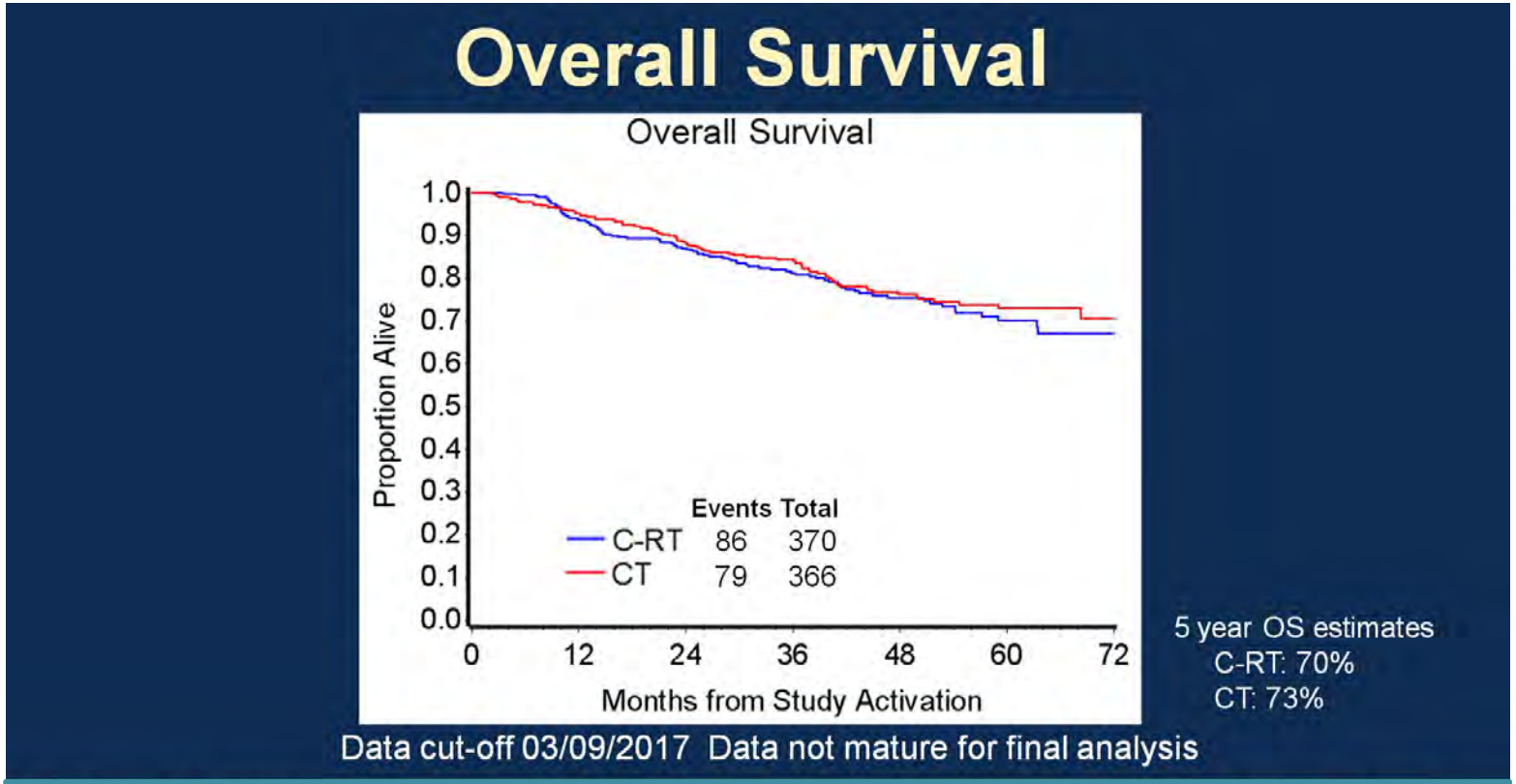

Também não houve vantagem em SG

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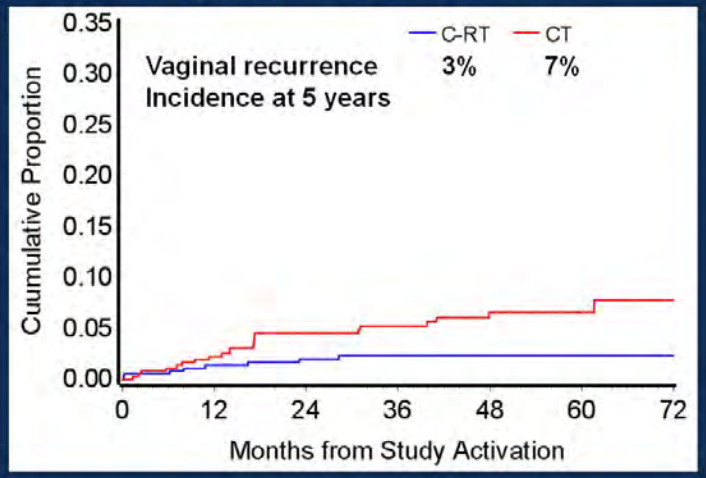
GOG 258

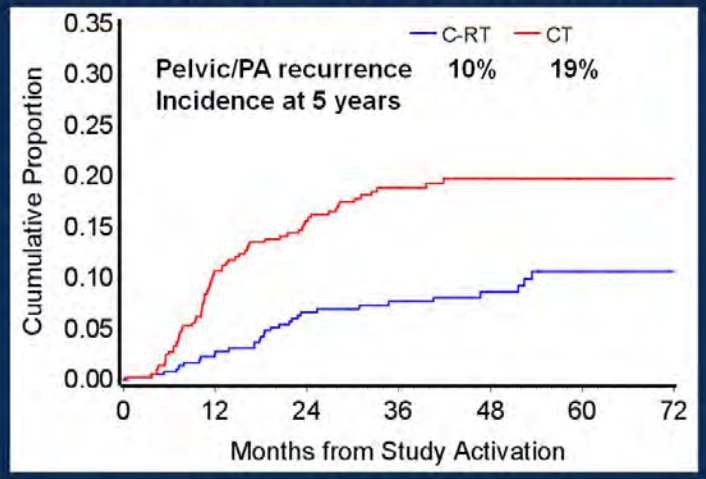
Cumulative Incidence of Recurrence

Vaginal Recurrence



C-RT vs. CT : HR=0.36 (CI: 0.16-0.82)

Pelvic and PA Recurrence



C-RT vs. CT : HR=0.43 (CI: 0.28-0.66)

As taxas de recorrências locais foram maiores para o grupo que não recebeu radioterapia, como era de se esperar.

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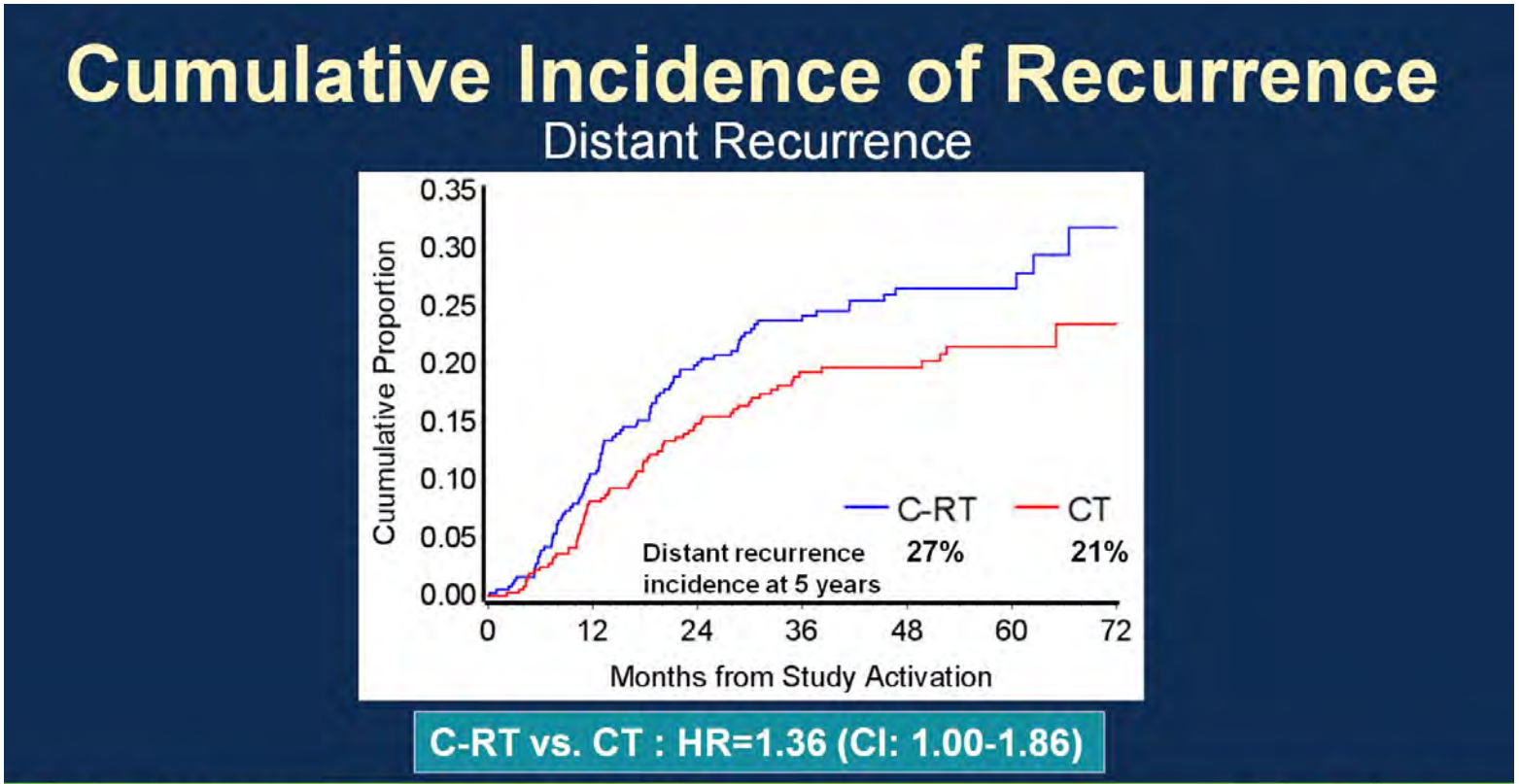

Mas as recorrências à distância foram maiores no grupo exposto a RT, o que no final igualou a SG e SLR

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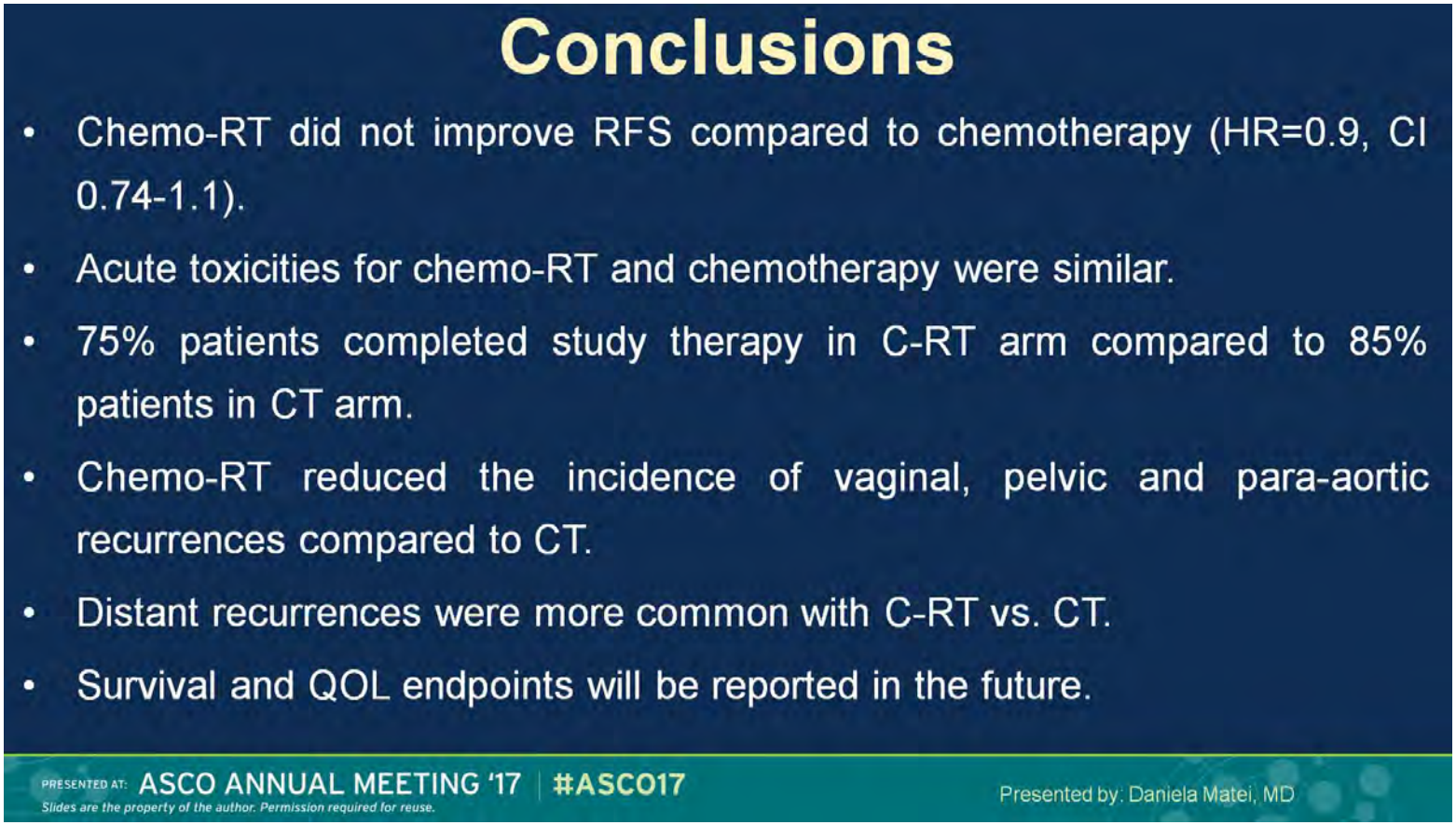
GOG 258



Presented By Daniela Matei at 2017 ASCO Annual Meeting

Docetaxel + Cisplatina ou Carbo + Taxol comparado com Cisplatina e Adriamicina no tratamento adjuvante do Ca de endométrio de alto risco

Presented By Hiroyuki Nomura at 2017 ASCO Annual Meeting

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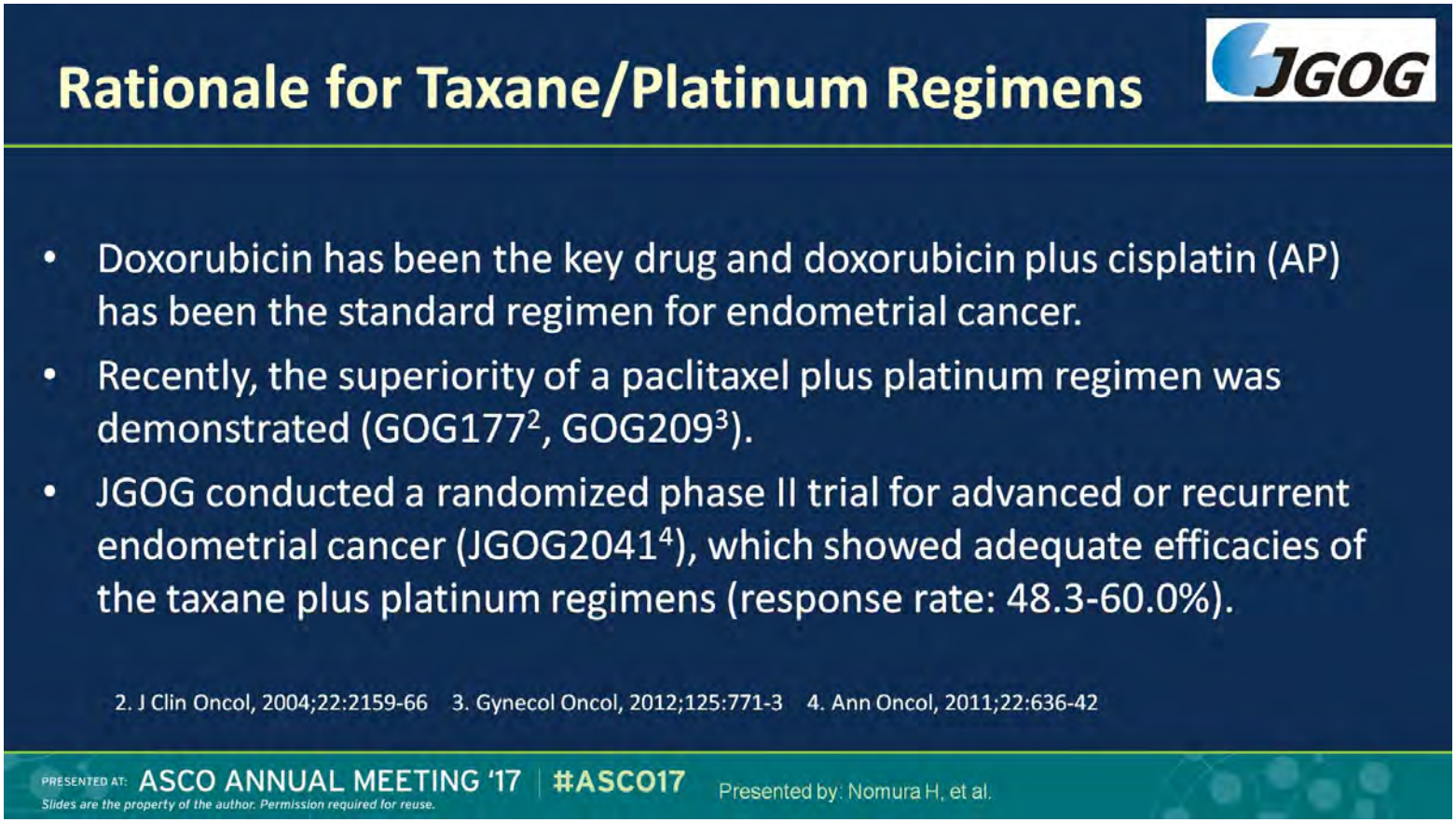
JGOG 2043



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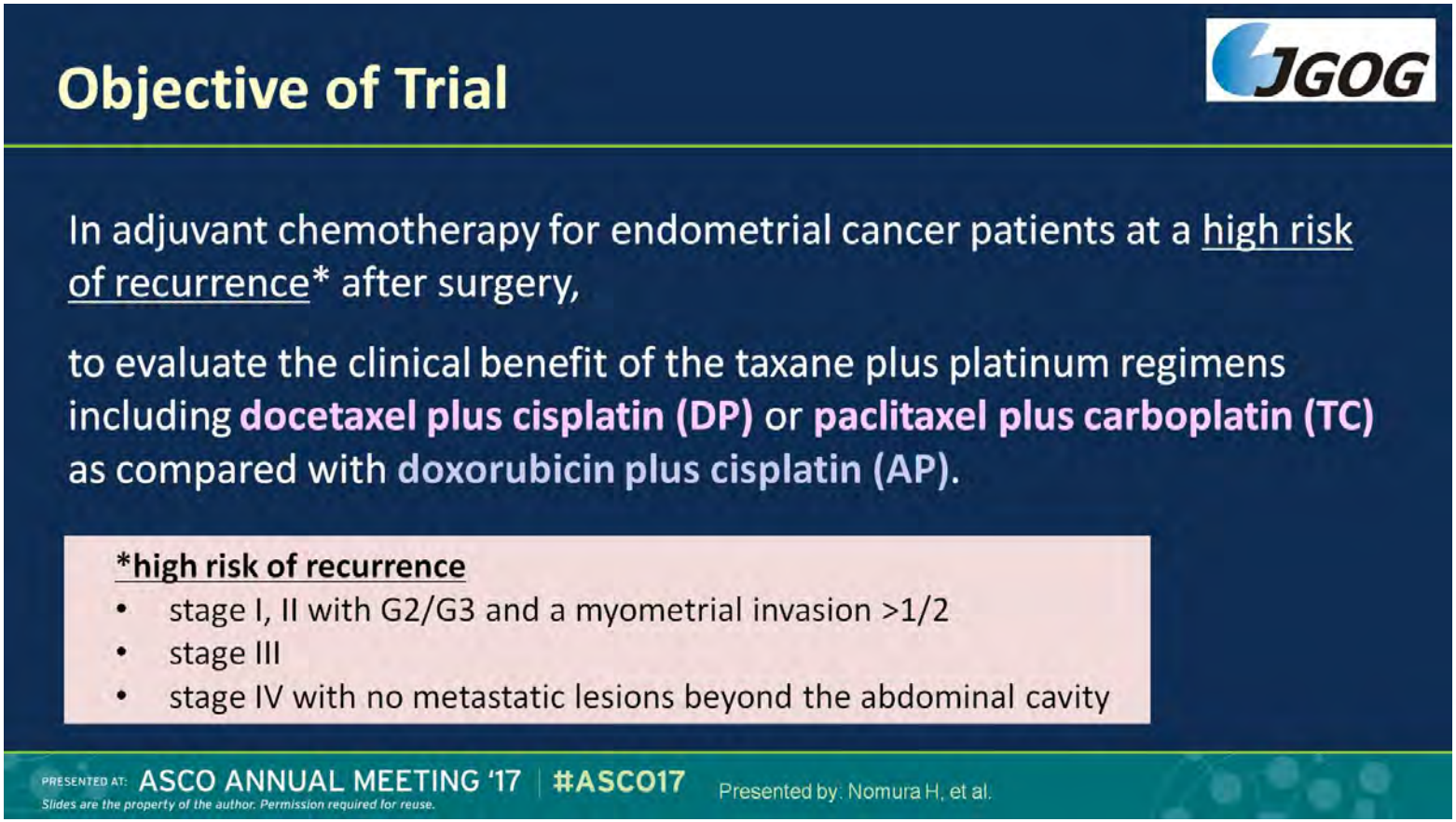

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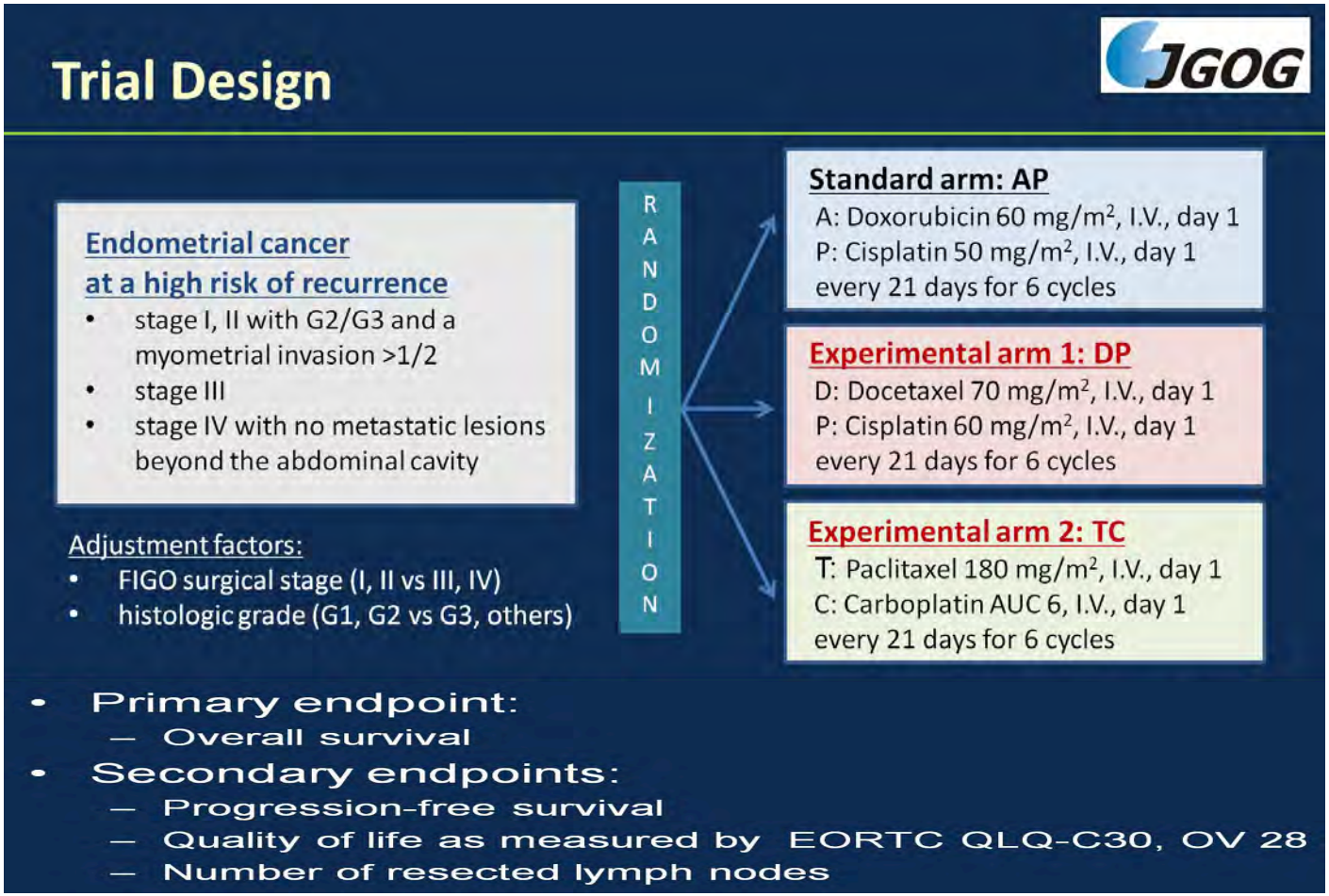

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Patient Characteristics (1)

Characteristics		AP (N=263) No. of patients (%)	DP (N=263) No. of patients (%)	TC (N=262) No. of patients (%)
Median age [range]		58.0 [22-74]	59.0 [29-74]	59.0 [31-74]
Performance status (ECOG)*	0	233 (88.6)	233 (88.6)	217 (82.8)
	1	28 (10.6)	27 (10.3)	39 (14.9)
	2	0 (0.0)	1 (0.4)	3 (1.1)
Surgical stage (FIGO 1988)	IC	54 (20.5)	59 (22.4)	58 (22.1)
	II	26 (9.9)	21 (7.9)	24 (9.2)
	III	167 (63.5)	169 (64.3)	158 (60.3)
	IV	16 (6.1)	14 (5.3)	22 (8.4)
Histologic type	Endometrioid	218 (82.9)	213 (80.9)	202 (77.1)
	Serous	20 (7.6)	17 (6.5)	20 (7.6)
	Clear	7 (2.7)	9 (3.4)	9 (3.4)
	Mixed / Others	18 (6.8)	24 (9.0)	31 (11.8)
Histologic grade	1	62 (23.6)	68 (25.9)	61 (23.3)
	2	108 (41.1)	98 (37.3)	105 (40.1)
	3	71 (27.0)	74 (28.1)	65 (24.8)
	Unknown	22 (8.3)	23 (8.7)	31 (11.9)
Size of residual tumor	No residual	253 (96.2)	253 (96.2)	251 (95.8)
	< 1 cm	5 (1.9)	4 (1.5)	5 (1.9)
	≥ 1 cm	5 (1.9)	6 (2.3)	6 (2.3)

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Treatment Tolerability

Tolerability		AP (N=263) No. of patients (%)	DP (N=263) No. of patients (%)	TC (N=262) No. of patients (%)
Completed protocol treatment		210 (79.8)	218 (82.9)	199 (76.0)
Discontinued due to:	Progressive disease / Deaths	5 (1.9)	6 (2.3)	3 (1.1)
	Adverse events (AEs)	17 (6.5)	15 (5.7)	32 (12.2)
	Patients withdrawal or refusal	26 (9.9)	19 (7.2)	23 (8.8)
	Others	5 (1.9)	5 (1.9)	5 (1.9)
Delayed administration		188 (72.0)	108 (41.4)*	180 (69.5)
Dose reduction		77 (29.5)	56 (21.5)**	72 (27.8)
Relative dose intensity (average)		A: 86.7% P: 88.5%	D: 92.6% P: 92.9%	T: 86.4% C: 87.5%

Fisher's exact test, *P<0.0001, **P=0.05

No grupo de DOCETAXEL + CISPLATINA houve menos atraso na administração de doses e menor necessidade de redução de doses.

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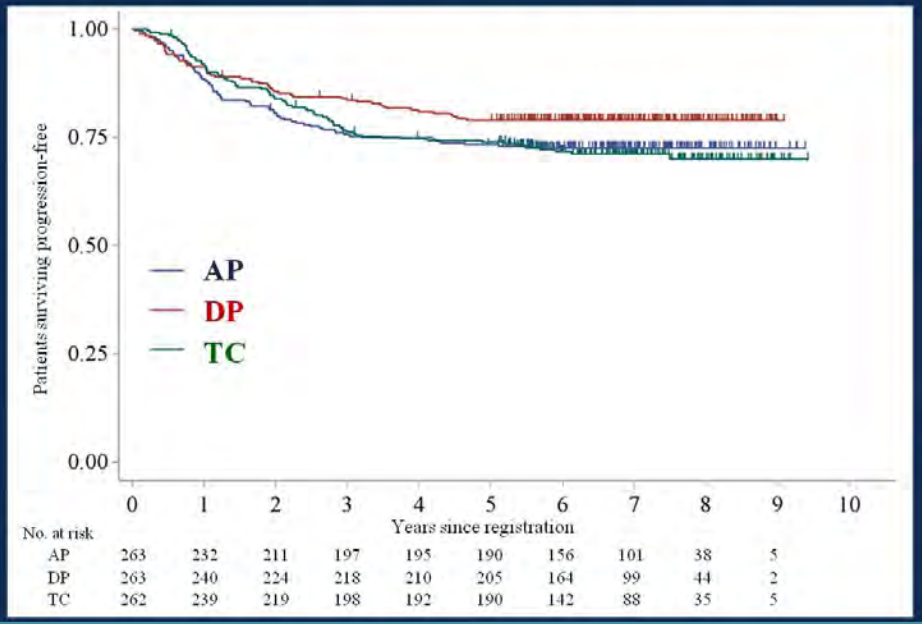
Progression-free Survival (PFS)



Arm	N	Events	5-yr PFS	Log-rank test
AP	263	72	74.5%	
DP	263	55	80.5%	P=0.1246
TC	262	75	74.3%	

Note:
For cases with no events, they were censored at the latest survival date.

Nenhum dos esquemas mostrou-se estatisticamente superior ao outro, em termos de SLP. Apesar de numericamente esse número ter sido maior para o esquema DP

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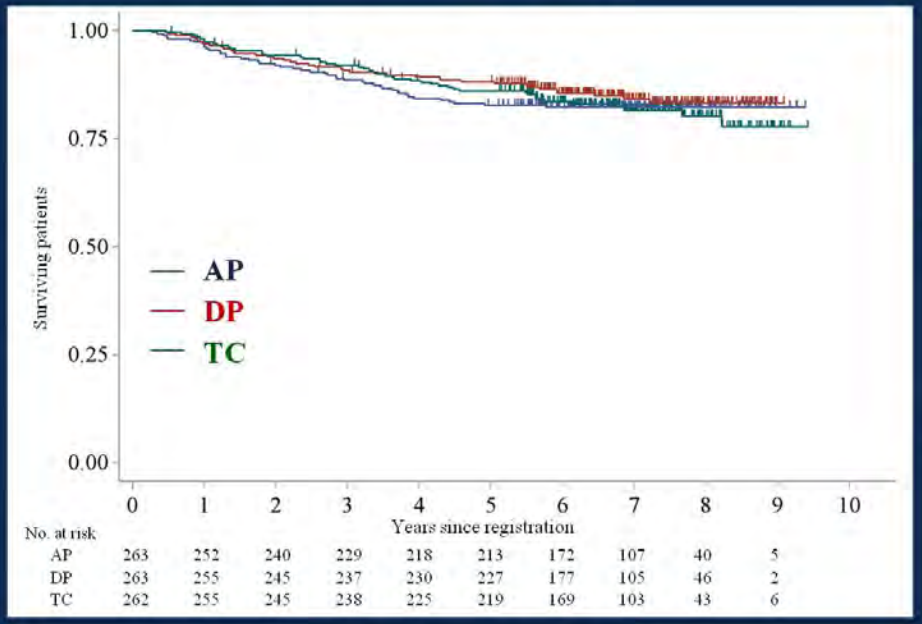
Overall Survival (OS)



Arm	N	Events	5-yr OS	Log-rank test
AP	263	46	83.9%	
DP	263	40	88.9%	P=0.6734
TC	262	47	88.0%	

Note:
For cases with no events, they were censored at the latest survival date.

Não houve também superioridade estatística para nenhum dos esquemas, em relação a Sobrevida Global.

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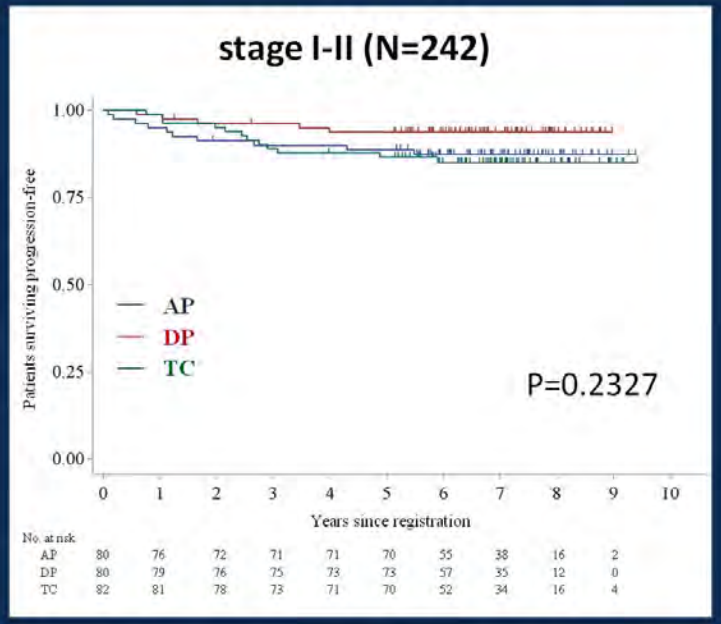
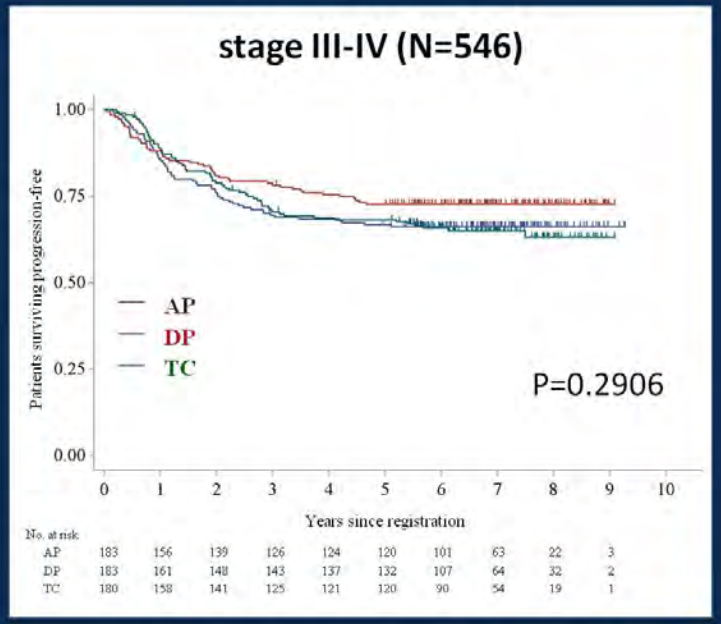
Effect of FIGO surgical stage on PFS





Na estratificação por Estágio clínico também não se observaram diferenças significativas em SLP.

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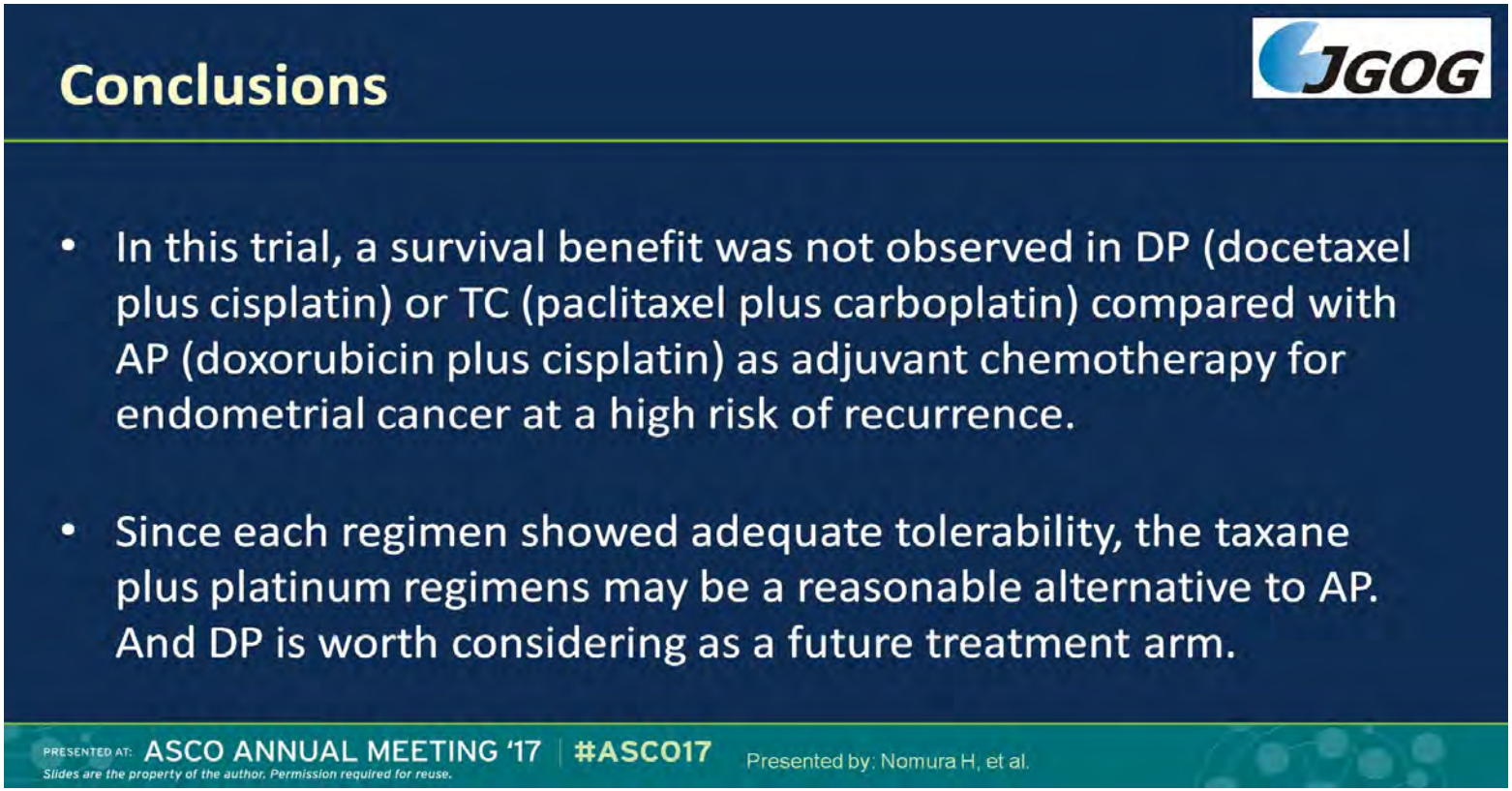

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Câncer de Colo Uterino, Vagina e Vulva

Nivolumabe em Câncer de colo uterino, vagina e vulva recorrentes/metastáticos

An Open-label, Multicohort, Phase 1/2 Study of Nivolumab in Patients With Virus-Associated Tumors (CheckMate 358): Efficacy and Safety in Recurrent or Metastatic Cervical, Vaginal, and Vulvar Cancers

Antoine Hollebecque,[1] Tim Meyer,[2] Kathleen Nadine Moore,[3] Jean-Pascal Machiels,[4] Jacques De Grève,[5] José Maria López-Picazo,[6] Ana Oaknin,[7] Joseph Kerger,[8] Valentina Boni,[9] Jeff Evans,[10] Rebecca Kristeleit,[2] Shangbang Rao,[11] Ibrahima Soumaoro,[11] Alexander Cao,[11] Suzanne L. Topalian[12]

[1]Gustave Roussy Cancer Institute, Villejuif, France; [2]University College London Cancer Institute, London, UK; [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [4]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [5]Vrije Universiteit Brussel, Brussels, Belgium; [6]University Clinic of Navarra, Pamplona, Spain; [7]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [8]Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; [9]START Madrid-CIOCC Hospital Universitario HM Sanchinarro, Madrid, Spain; [10]University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [11]Bristol-Myers Squibb, Princeton, NJ, USA; [12]The Sidney Kimmel Comprehensive Cancer Center and Bloomberg~Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD, USA

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CheckMate 358

Background

- Recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers have a high unmet need and poor prognosis
- Second-line treatment options for R/M cervical cancer result in median progression-free survival (PFS) of ~2–4 months and objective response rates (ORR) of 0–14%[1]
- Human papillomavirus (HPV) infection is causative in over 90% of cervical, 75% of vaginal, and 69% of vulvar cancers[2]
  - HPV can evade host immune surveillance, through increased expression of programmed death ligand 1 (PD-L1), enabling viral persistence and the development of malignant lesions[3–6]
  - PD-L1 has been shown to be a biomarker of HPV infection of the cervix and is significantly upregulated in cervical cancer[7]
- Nivolumab, a PD-1 inhibitor, has demonstrated antitumor activity in several tumor types, and the role of immunotherapy is evolving in gynecologic malignancies

1. Yu S, Garcia AA. *Am J Hemat Oncol* 2015;11:26–31. 2. Viens LJ, et al. *MMWR Morb Mortal Wkly Rep* 2016;65:661–666. 3. Westrich JA, et al. *Virus Res* 2017;231:21–33. 4. Song D, et al. *Oncol Lett* 2015;10:600–606. 5. Xie Z, et al. *Immunol Invest* 2009;38:624–638. 6. Liu C, et al. *Mol Med Rep* 2017;15:1063–1070. 7. Mezache L, et al. *Mod Pathol* 2015;28:1594–1602.

O HPV é capaz de promover *upregulation* do PD-L1 em células tumorais.

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CheckMate 358

CheckMate 358 Study Design: Metastatic Monotherapy Cohort

- CheckMate 358 (NCT02488759) is an ongoing, open-label, phase 1/2, multicohort study

Eligibility

Eligible tumor types
- EBV+ gastric carcinoma
- HPV+ SCCHN
- Cervical, vaginal, and vulvar cancers
- Merkel cell carcinoma
- Nasopharyngeal carcinoma

Key eligibility criteria
- ≤2 prior treatments for R/M disease
- ≥1 target lesion[a]
- ECOG PS: 0–1
- PD-L1 unselected

Treatment

Nivolumab 240 mg Q2W until progression or unacceptable toxicity

Assessments
- Imaging Q8W for the first year of treatment
- Imaging Q12W thereafter

Follow-up
- Minimum follow-up: 12 weeks
- Survival follow-up

- **Primary endpoints**: ORR[a]
- **Secondary endpoints**: DOR, PFS, OS

- Enrollment dates: October 2015 to February 2016
- Data cutoff: July 2016 (median follow-up: 31 weeks)

[a]Per investigator-assessed RECIST v1.1 criteria
DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group; EBV = Epstein-Barr virus; OS = overall survival; QXW = every X weeks; RECIST = Response Evaluation Criteria In Solid Tumors; SCCHN = squamous cell carcinoma of the head and neck

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CheckMate 358

Demographics and Disease Characteristics

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	Patients (N = 24)
Age, median (range), years	51 (28–78)
Region, n (%)	
North America	1 (4.2)
Europe	23 (95.8)
ECOG PS, n (%)[a]	
0	11 (45.8)
1	12 (50.0)
Tumor type, n (%)	
Cervical	19 (79.2)
Vaginal/vulvar	5 (20.8)
Number of prior systemic therapies in R/M setting, n (%)	
0	7 (29.2)
1	10 (41.7)
2	7 (29.2)
HPV status, n (%)[b]	
Positive	14 (58.3)
Not reported	10 (41.7)
Tumor PD-L1 expression, n (%)	
≥1%	10 (41.7)
<1%	3 (12.5)
Not tested	10 (41.7)
Not evaluable	1 (4.2)

[a]ECOG PS not reported in 1 patient at time of data cutoff; [b]Per local site testing

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CheckMate 358

Best Overall Response

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	All patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)
Best overall response, n (%)			
Complete response	1 (4.2)	1 (5.3)	0
Partial response	4 (16.7)	4 (21.1)	0
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)
ORR, n (%) [95% CI]	5 (20.8) [7.1, 42.2]	5 (26.3) [9.1, 51.2]	0 [0.0, 52.2]
Disease control rate, n (%)	17 (70.8)	13 (68.4)	4 (80.0)
Duration of response, median (range), months	NR[a] (0.0–5.8+)	NR[a] (0.0–5.8+)	NA

Taxas de resposta jamais vistas anteriormente, assim como impressionantes taxas de controle da doença e longos períodos de resposta sustentada

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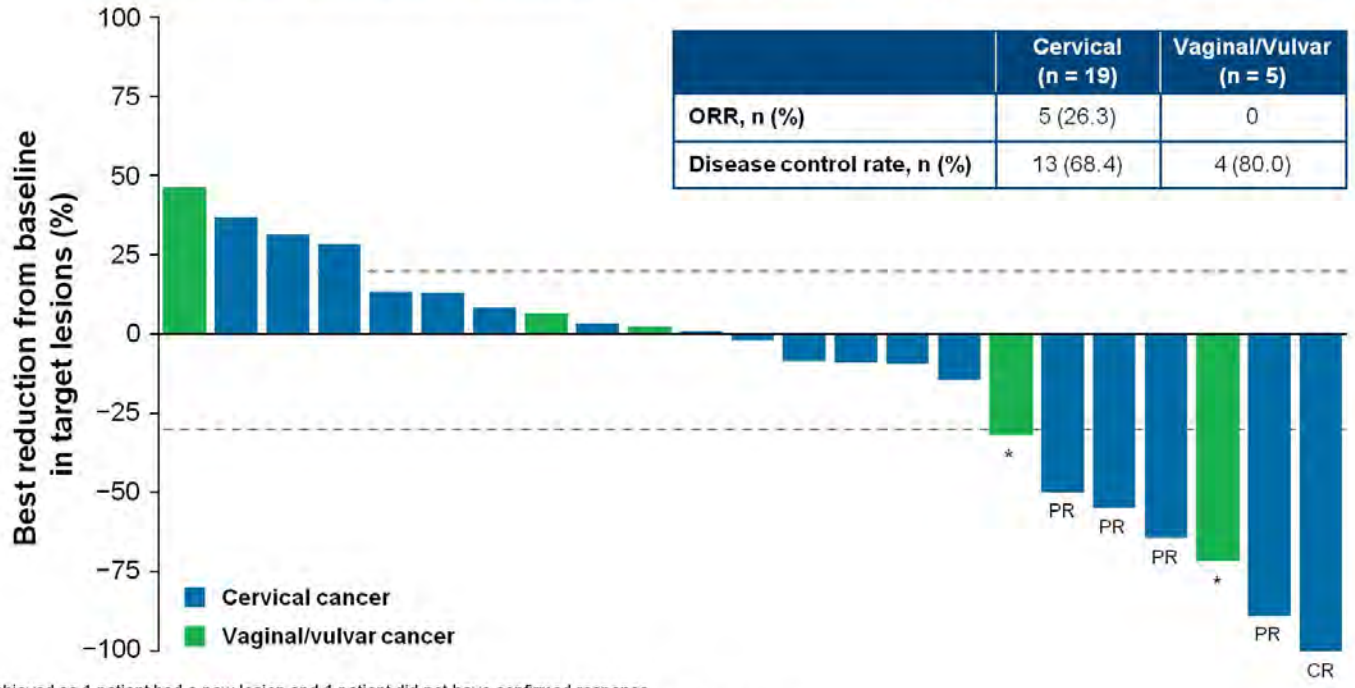
CheckMate 358

Best Reduction in Target Lesions

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	Cervical (n = 19)	Vaginal/Vulvar (n = 5)
ORR, n (%)	5 (26.3)	0
Disease control rate, n (%)	13 (68.4)	4 (80.0)



*PR not achieved as 1 patient had a new lesion and 1 patient did not have confirmed response
1 patient is not shown due to unavailable postbaseline tumor assessment prior to subsequent anti-cancer therapy
CR = complete response; PR = partial response

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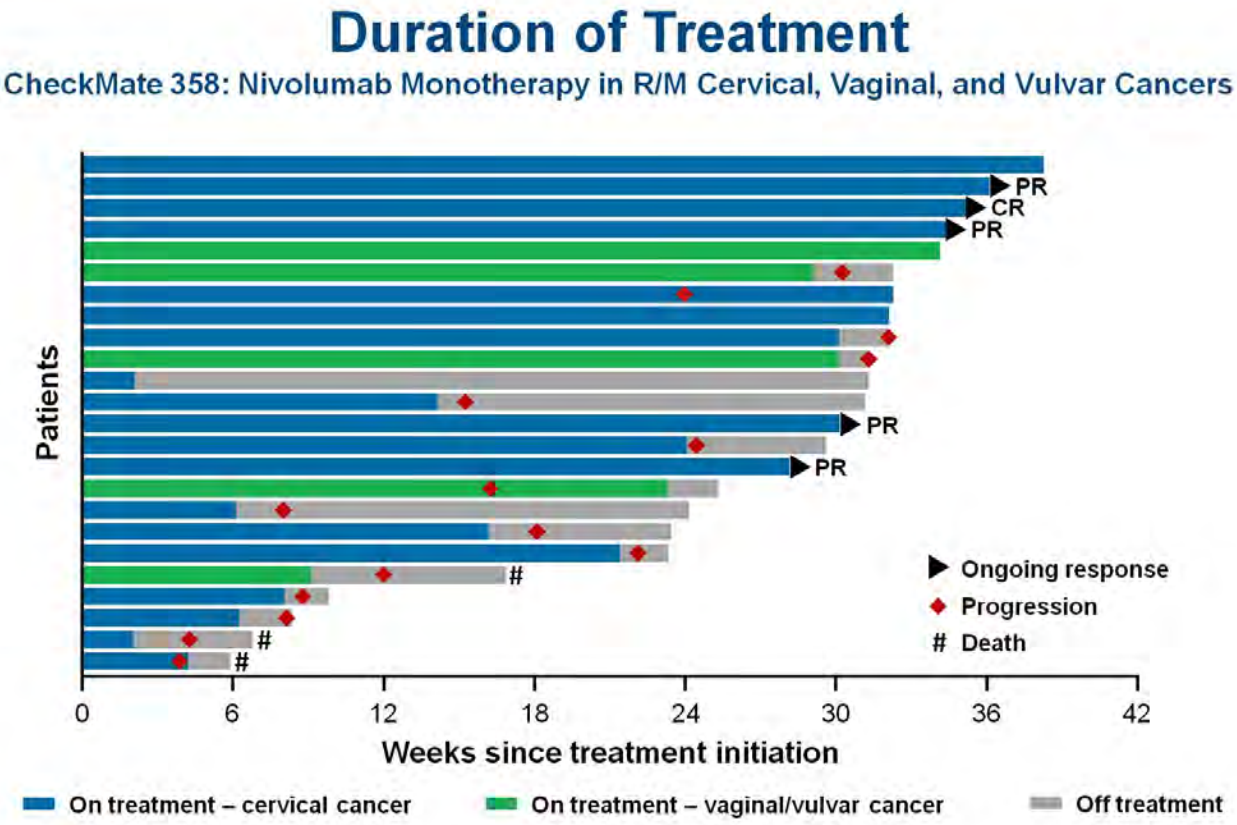

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CheckMate 358

Best Overall Response by Prior Systemic R/M Therapies

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	0 prior systemic therapies in R/M setting (n = 7)	≥1 prior systemic therapies in R/M setting (n = 17)
Best overall response, n (%)		
Complete response	0	1 (5.9)
Partial response	2 (28.6)	2 (11.8)
Stable disease	3 (42.9)	9 (52.9)
Progressive disease	2 (28.6)	5 (29.4)
ORR, n (%) [95% CI]	2 (28.6) [3.7, 71.0]	3 (17.6) [3.8, 43.4]
Disease control rate, n (%)	5 (71.4)	12 (70.6)

As respostas foram melhores nas pacientes virgens de tratamento prévio no cenário recorrente/metastático

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CheckMate 358

Best Overall Response by PD-L1 and HPV

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	PD-L1 expression		HPV status[a]	
	PD-L1 ≥1% (n = 10)	PD-L1 <1% (n = 3)	Positive (n = 14)	Not reported (n = 10)
Best overall response, n (%)				
Complete response	1 (10.0)	0	0	1 (10.0)
Partial response	1 (10.0)	1 (33.3)	4 (28.6)	0
Stable disease	6 (60.0)	1 (33.3)	4 (28.6)	8 (80.0)
Progressive disease	2 (20.0)	1 (33.3)	6 (42.9)	1 (10.0)
ORR, n (%) [95% CI]	2 (20.0) [2.5, 55.6]	1 (33.3) [0.8, 90.6]	4 (28.6) [8.4, 58.1]	1 (10.0) [0.25, 44.5]
Disease control rate, n (%)	8 (80.0)	2 (66.7)	8 (57.1)	9 (90.0)

As respostas correlacionam-se tanto com a expressão de PD-L1 quanto com a infecção por HPV.

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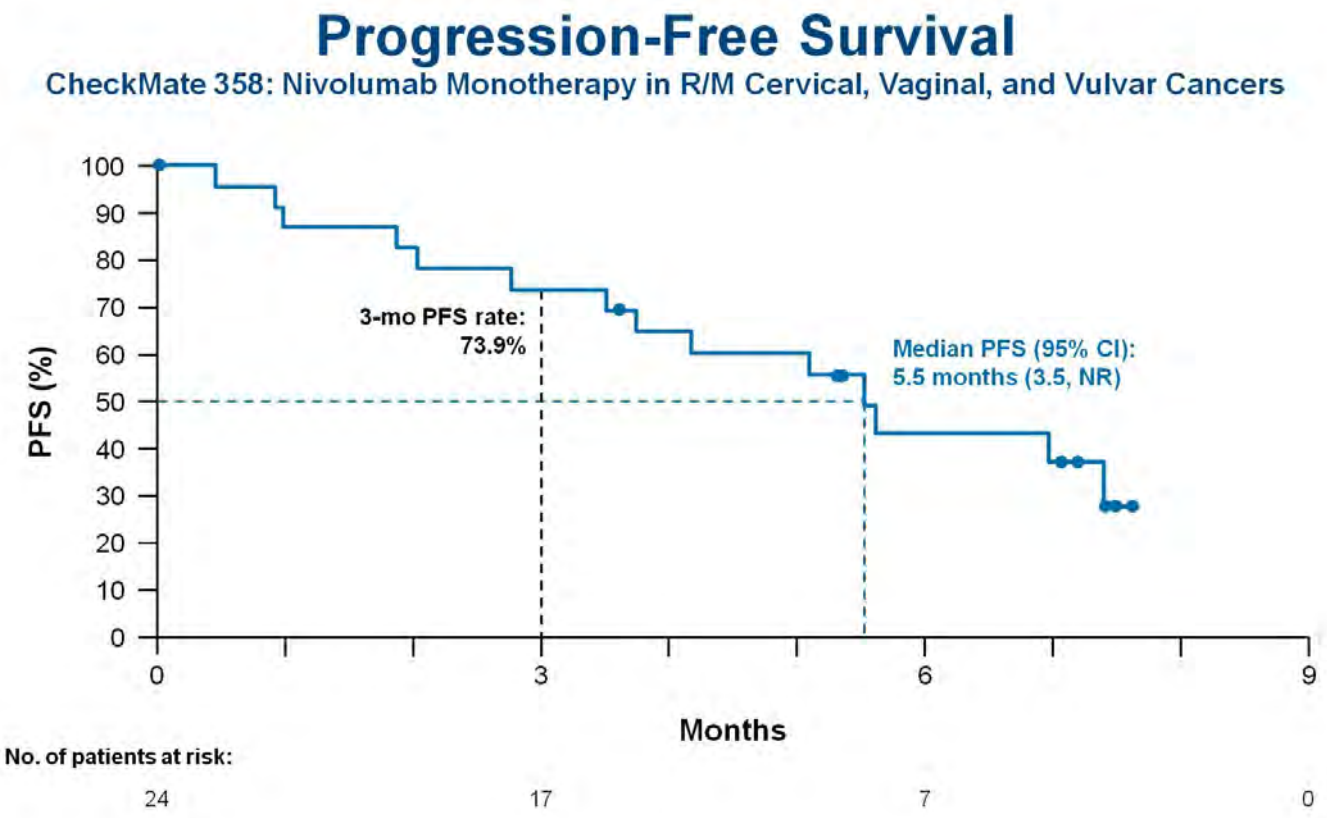

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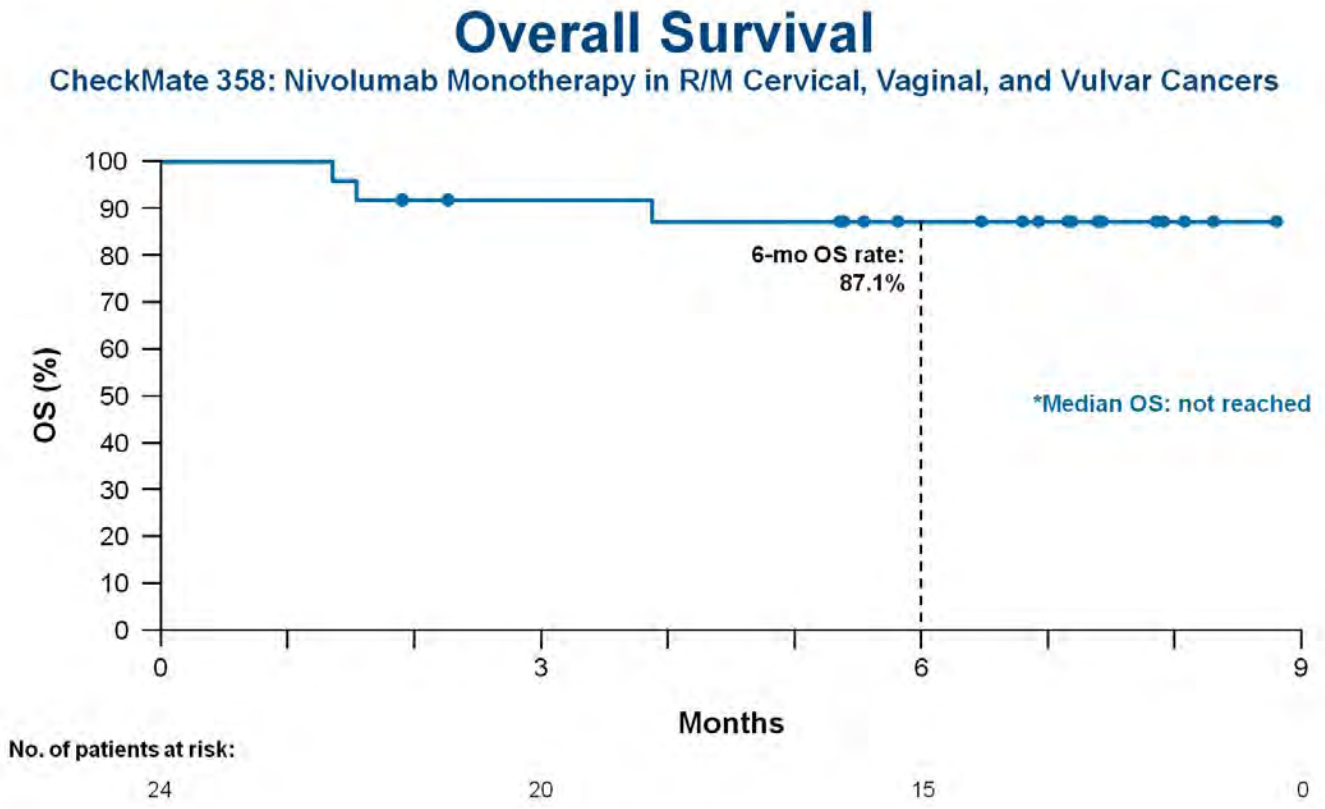

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CheckMate 358

Treatment-Related Adverse Events

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

	All patients (N = 24)	
	Any grade	Grade 3–4
Any TRAE, n (%)	17 (70.8)	3 (12.5)
TRAEs in >1 patient, n (%)		
Diarrhea	4 (16.7)	1 (4.2)
Fatigue	4 (16.7)	0
Arthralgia	3 (12.5)	0
Decreased appetite	3 (12.5)	0
Pruritus	2 (8.3)	0
Dry eye	2 (8.3)	0
Hypothyroidism	2 (8.3)	0

- Other grade 3–4 TRAEs were hyponatremia, syncope, and hepatocellular injury
- No treatment-related deaths occurred

TRAE = treatment-related adverse event

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Conclusions

CheckMate 358: Nivolumab Monotherapy in R/M Cervical, Vaginal, and Vulvar Cancers

- Nivolumab demonstrated encouraging clinical activity in patients with R/M cervical, vaginal, and vulvar cancers
  - 20.8% ORR (all 5 responses in patients with cervical cancer at time of data cutoff)
    - Responses observed across tumor PD-L1 expression
  - 70.8% disease control rate
  - Median OS was not reached; 6-month OS rate was 87.1%
- The observed safety profile was manageable and consistent with previous results seen with nivolumab monotherapy in other tumor types
- These data support further evaluation of nivolumab in these patients, including in combination with other therapies

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