





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 os 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



○ CONFLITOS DE INTERESSE

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



ROTEIRO

1. Câncer de Ovário

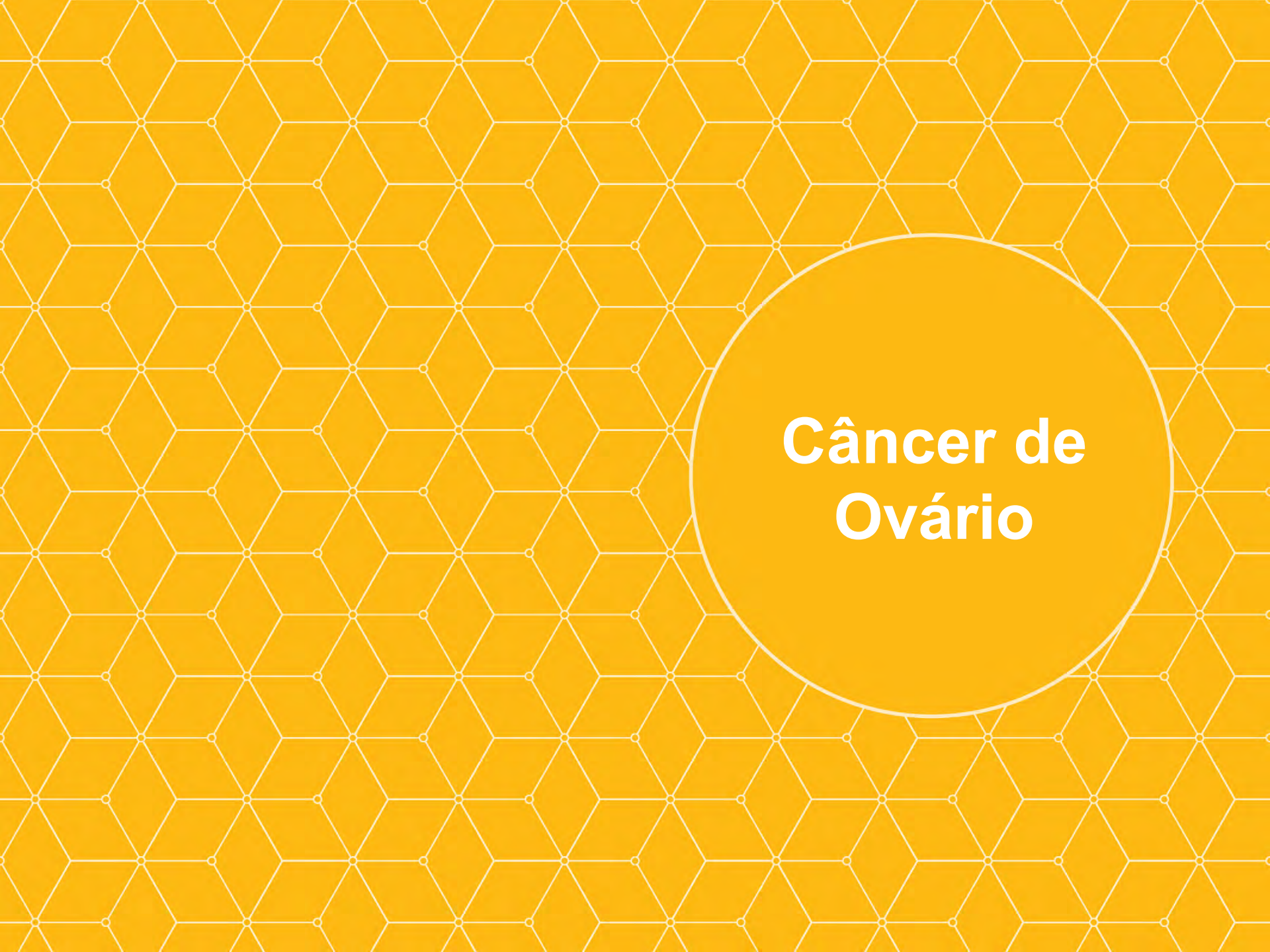
- Existe papel para linfadenectomia profilática?
- Qual o papel da cirurgia Citorredutora secundária na recorrência?
- Olaparibe de manutenção: Qual o impacto na Qualidade de vida?
- Há papel para Bevacizumabe Neoadjuvante em pacientes que farão cirurgia de intervalo?

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?

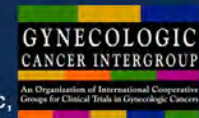
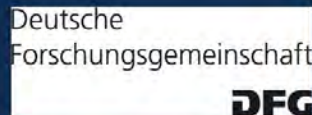
Abstr. 5500: LION – LYMPHADENECTOMY IN OVARIAN NEOPLASMS.

A prospective randomized AGO Study Group led Gynecologic Cancer Intergroup trial. AGO OVAR OP3/ENGOT-ov31.

Philipp Harter¹, J. Sehouli², D. Lorusso³, A. Reuss⁴, I. Vergote⁵, C. Marth⁶, JW Kim⁷, F. Raspagliesi⁸, B. Lampe⁹, F. Landoni¹⁰, W. Meier¹¹, D. Cibula¹², A. Mustea¹³, S. Mahner¹⁴, I. Runnebaum¹⁵, B. Schmalfeldt¹⁶, A. Burges¹⁴, R. Kimmig¹⁷, U. Wagner¹⁸, A. du Bois¹

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Methods II: Main inclusion criteria

(Pre-operative criteria)

- Suspected or already proven diagnosis of advanced epithelial invasive cancer of the ovaries, tubes, or peritoneum FIGO IIB-IV (FIGO IV only if deemed resectable)
- Good performance status (ECOG 0/1)
- Age 18-75 years
- Macroscopic complete resection seems possible
- Clinical / radiological negative pelvic and para-aortic lymph nodes
- No prior chemotherapy
- No prior dissection of lymph nodes

Não poderia haver suspeita de acometimento linfonodal clínica ou radiológica

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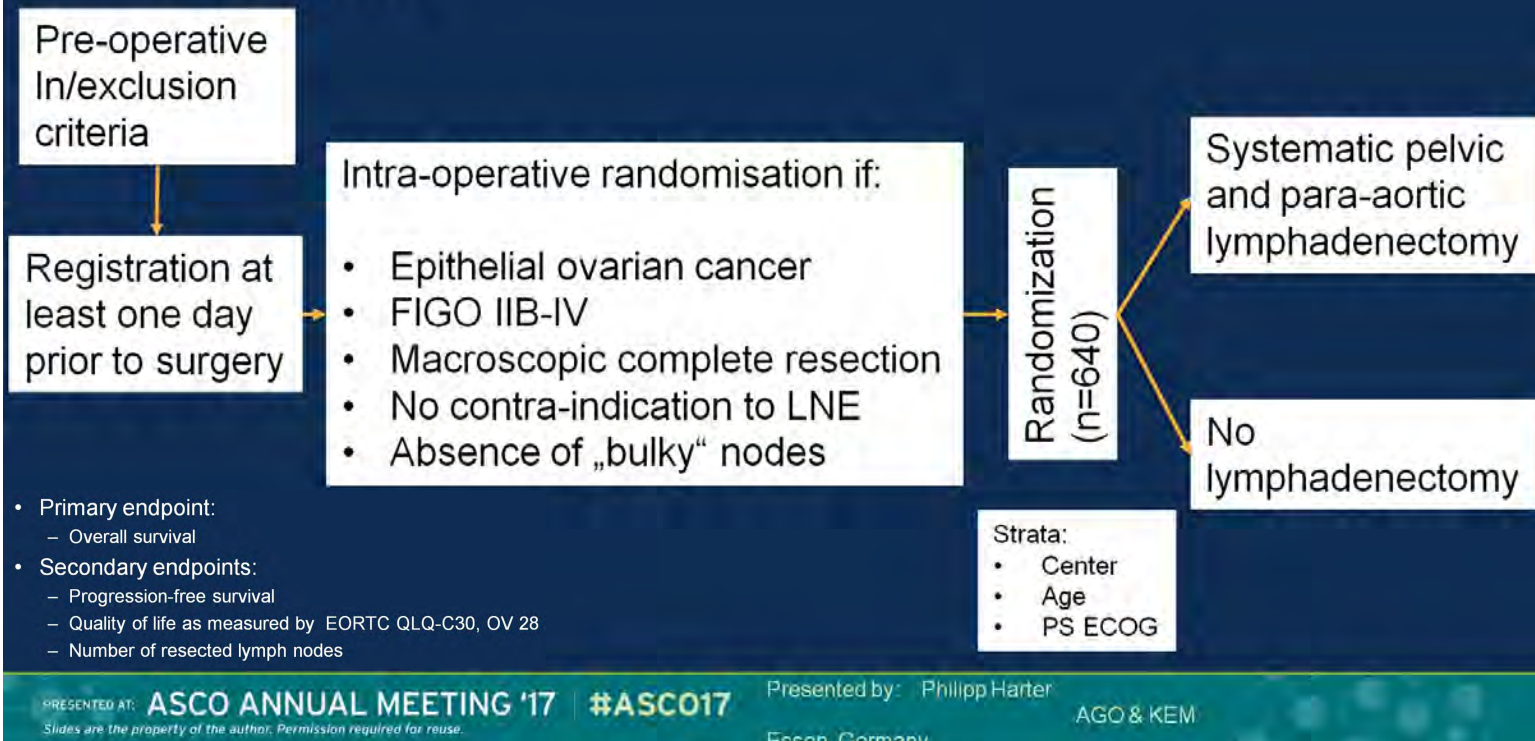
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LION trial

Design: LION



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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	272 (84.2)	280 (86.4)	0.43
ECOG 1	51 (15.8)	44 (13.6)	
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	304 (94.1)	303 (93.5)	0.75
Others	19 (5.9)	21 (6.5)	
Final FIGO stage*			
I-IIA	15 (4.6)	17 (5.2)	0.32
IIB-IIIA	41 (12.7)	52 (16.0)	
III-IV	261 (80.8)**	244 (75.3)***	
missing	6 (1.9)	11 (3.4)	
Histology:			
G2/3 serous	234 (72.4)	227 (70.1)	0.54
others	89 (27.6)	97 (29.9)	

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	291 (90.1)	291 (89.8)	0.99
• Pelvis	276 (85.5)	278 (85.8)	
• Paracolic	193 (59.8)	208 (64.2)	
• Diaphragm	173 (53.6)	196 (60.5)	
Gastrointestinal tract resection	169 (52.3)	167 (51.5)	0.84
Stoma	34 (10.5)	24 (7.4)	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	7 (2.1)	7 (2.1)	0.99
Partial hepatectomy	27 (8.4)	28 (8.6)	0.90
Pleurectomy	20 (6.2)	24 (7.4)	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)	57 (45-73)			
Para-aortic LN	22 (16-33)			
Pelvic LN	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	205 (63.7)	181 (56.0)	+ 8%	0.005
Massive transfusions (> 10 RBC/24h)	7 (2.2)	2 (0.6)		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

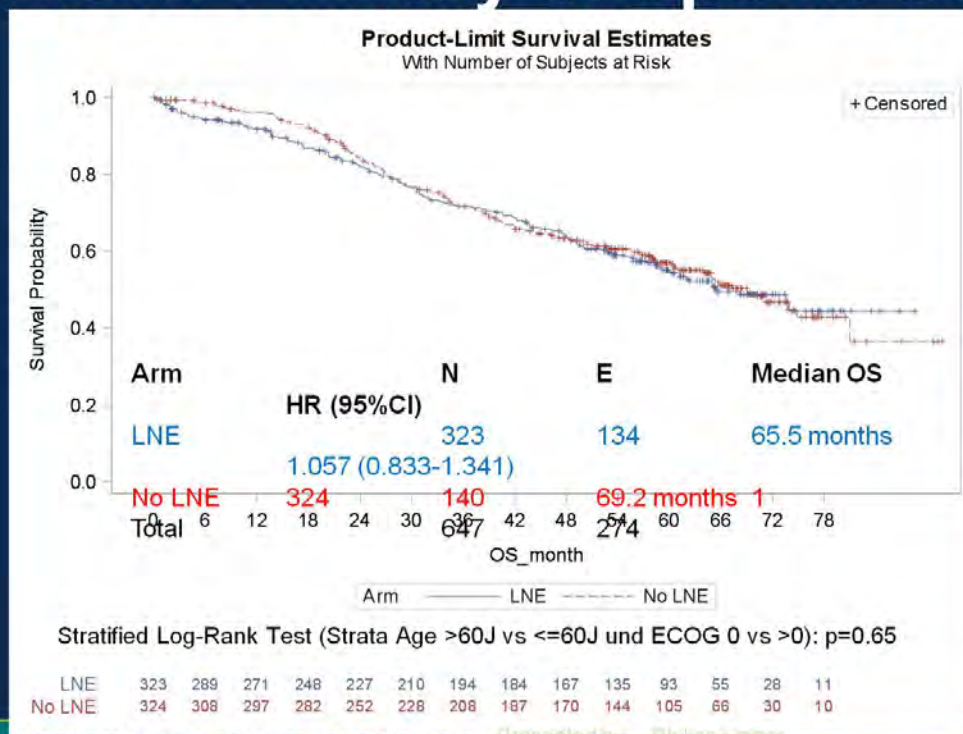
	LNE (%)	No LNE (%)	p-value
Infections requiring antibiotics	83 (25.8)	60 (18.6)	0.03
Fever > 38.0° Celsius	41 (12.7)	32 (9.9)	0.21
Sepsis	6 (1.9)	3 (0.9)	0.31
Thrombosis	7 (2.2)	5 (1.6)	0.56
Pulmonary embolism	12 (3.7)	15 (4.6)	0.56
Secondary wound healing	31 (9.6)	19 (5.9)	0.12
Prolonged ileus (conservative 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

LION: Primary endpoint OS

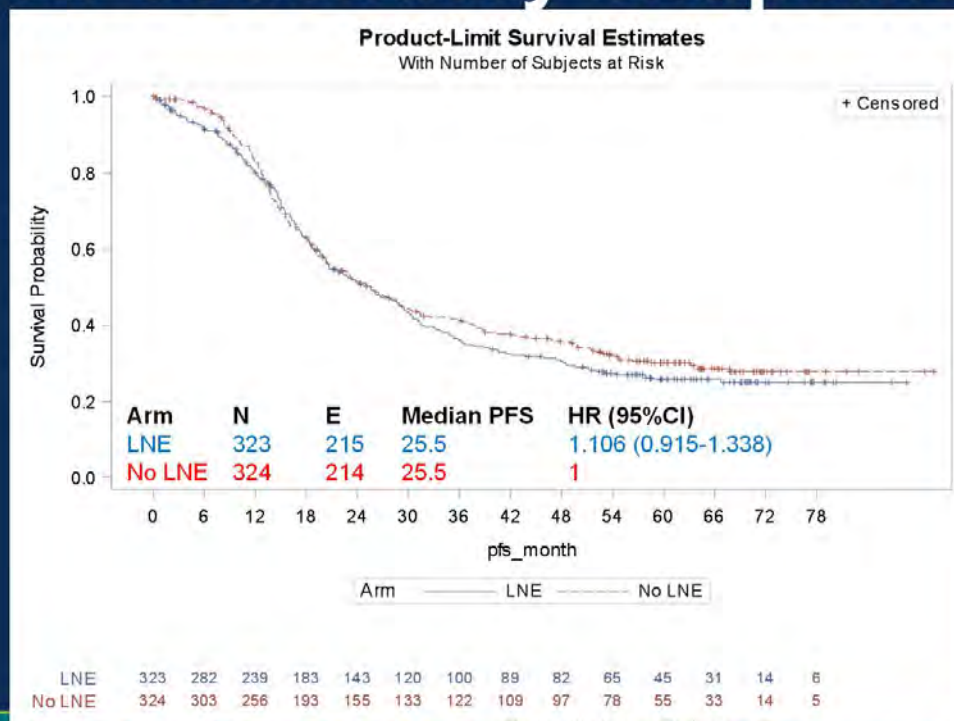


A linfadenectomia profilática de rotina não foi capaz de aumentar a SG

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LION trial

LION: Secondary endpoint PFS

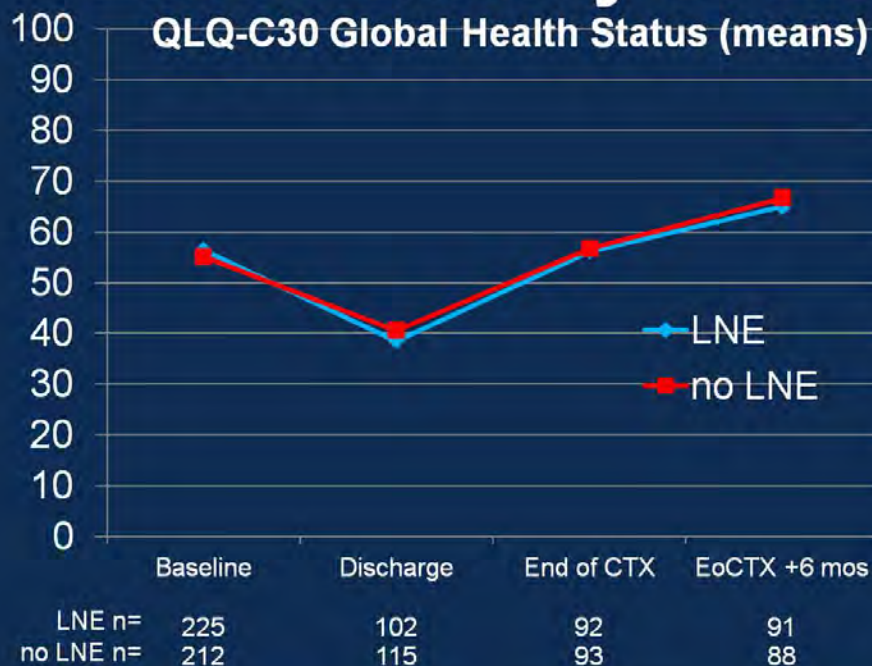


O Objetivo secundário de SLP também não foi alcançado

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LION trial

LION: Quality of Life



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

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LION: Conclusions

- Patients with complete resection during upfront surgery and treated in quality assured centres have an excellent prognosis (median OS ~ 67.2 months; median PFS ~ 25.5 months)
- Systematic pelvic and para-aortic LNE in patients with advanced ovarian cancer with both intra-abdominal complete resection and clinically negative LN neither improve overall nor progression-free survival
....despite detecting (and removing) sub-clinical retroperitoneal lymph node metastases in 56% of patients.
- Our data indicate that systematic LNE of clinical negative LN in patients with advanced ovarian cancer and complete resection should be omitted.

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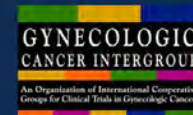
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Qual o papel da cirurgia Citorredutora secundária no Ca de ovário recorrente?

*Abstr. 5501: Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: the interim analysis of **AGO DESKTOP III** / ENGOT ov20*

Andreas du Bois¹, I. Vergote², G. Ferron³, A Reuss⁴, W. Meier¹, S. Greggi⁵, P. Jensen⁶, F. Selle³, F. Guyon³, C. Pomet³, F. Lecuru³, R. Zang⁷, E. Avall-Lunqvist⁶, JW Kim⁸, J. Ponce⁹, F. Raspagliesi⁵, S. Ghaem-Maghami¹⁰, A. Reinthaller¹¹, P. Harter (PI)¹, and J. Sehouli¹

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⁴ KKS Marburg, Germany; ⁵ MITO & Naples, Milan, **Italy**;
⁶ NSGO & Odense, Stockholm, **Denmark & Sweden**; ⁷ SGOG & Shanghai, **China**;
⁸ KGOG & Seoul, **Korea**; ⁹ GEICO & Barcelona, **Spain**; ¹⁰ NCRI & London, **UK**;
¹¹ AGO-Austria & Wien, **Austria**



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DESKTOP 3 *trial*

Design: AGO DESKTOP III (ENGOT-ov20; NCT01166737)

*PSROC = Ca de ovário recorrente sensível a platina

Pts. with:

- 1st relapse
- PSROC *
- AGO Score +ve

- 80 centres in 12 countries
- Recruitment 9/2010 - 3/2015
- 407 of 409 pts evaluated (2 screening failures)

R
n = 408

Cytoreductive Surgery with max. effort for complete resection

Platinum-based Combination therapy
strongly recommended

No OP

Immediate Platinum-based Combination therapy
strongly recommended

OP
Allowed
3rd
line

- 1st endpoint OS; sequential testing foreseen due to lack of historical data:
 - planned interim analysis after 122 OS events with significance level set to $p = 0.0052$ for early unblinding (O'Brien-Fleming group sequential plan).
 - final analysis after 244 OS events in all 408 planned pts.
- important secondary endpoints:
 - PFS, resection rate, treatment burden (M'n'M)

This AGO Score consisted of (1) good PS (ECOG 0), (2) complete resection during 1st line therapy, and (3) ascites less than 500 ml.¹



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 2 nd 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 2^a 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)

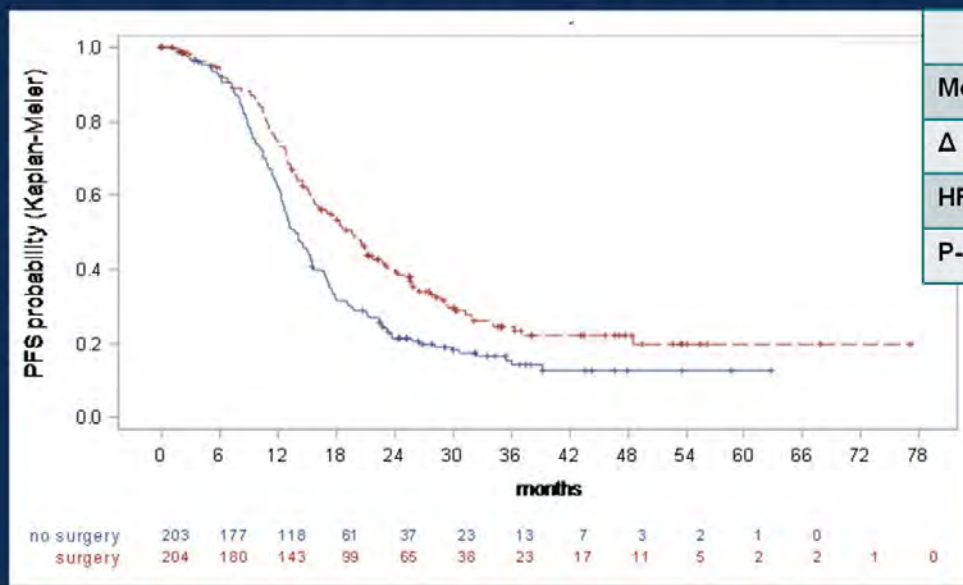
- The observed pooled 2-YSR was 83% and much higher than the assumed 2-YSR in the overall trial population.
- According to the trial protocol a planned interim analysis took place after observation of 122 OS events. This analysis did not reach the local significance level which was set to $\alpha=0.0052$ 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	

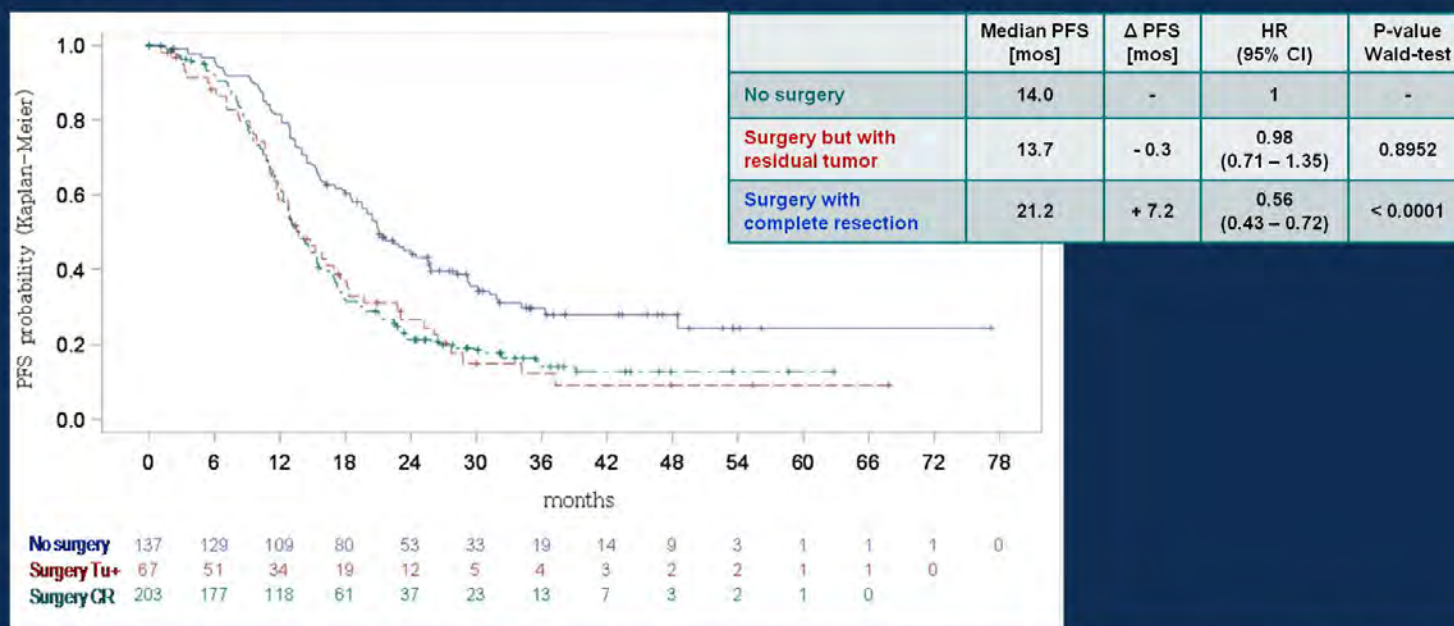
296 (73%) PFS events

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)

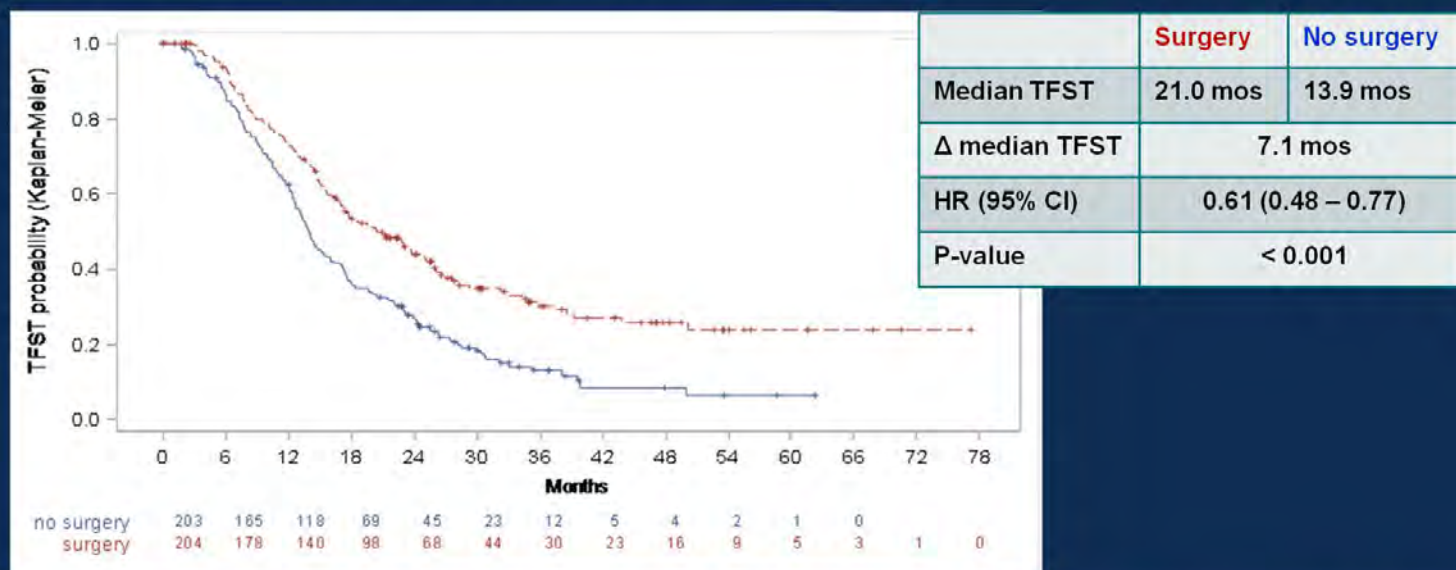


Pacientes com doença residual comportam-se como aqueles que não foram submetidos a cirurgia citorrredutora.

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DESKTOP 3 *trial*

AGO DESKTOP III: Outcome 5 (TFST = time to 3rd line) (AGO-OVAR OP.4; ENGOT-ov20; NCT01166737)



Esses resultados se traduzem em um tempo para 3^a 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 2 nd 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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AGO DESKTOP III: Conclusions

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

- **2nd cytoreductive surgery in pts with AGO Score positive PSROC resulted in a PFS and TFST advantage of 5.6 and 7.1 months which is at least comparable with all phase III trials in 2nd line therapy for PSROC so far.**
- **a benefit of surgery was exclusively seen in pts. with complete resection (CR) indicating the importance of selecting both:**
 - **the right centre with capability to achieve a CR in the majority of pts.**
 - **and the right pts (here: by AGO Score which selects app 50% of PSROC pts)**
- **hopefully, further follow-up will show that this benefit translates into OS**

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Presented by: **Andreas du Bois**

AGO & KEM

Essen, Germany

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

Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline (g) *BRCA*-mutated (m) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): SOLO2 Phase III trial

Michael Friedlander,¹ Val Gebski,² Emma Gibbs,² Ralph Bloomfield,³ Felix Hilpert,⁴ Lari B Wenzel,⁵ Florence Joly,⁶ Daniel Eek,⁷ Manuel Rodrigues,⁸ Andrew Clamp,⁹ Richard Penson,¹⁰ Diane Provencher,¹¹ Jacob Korach,¹² Tomasz Huzarski,¹³ Laura Vidal,¹⁴ Vanda Salutari,¹⁵ Clare Scott,¹⁶ Maria Ornella Nicoletto,¹⁷ Kenji Tamura,¹⁸ Eric Pujade-Lauraine¹⁹

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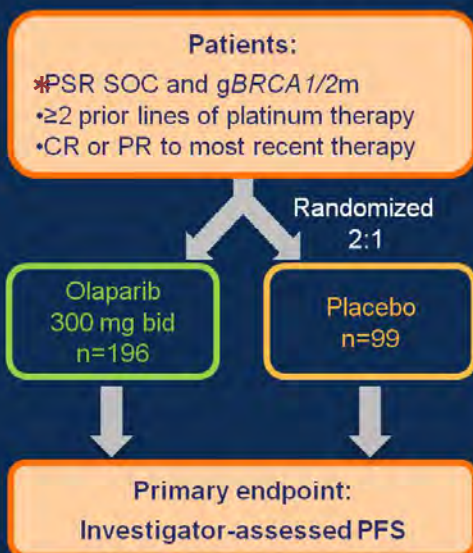
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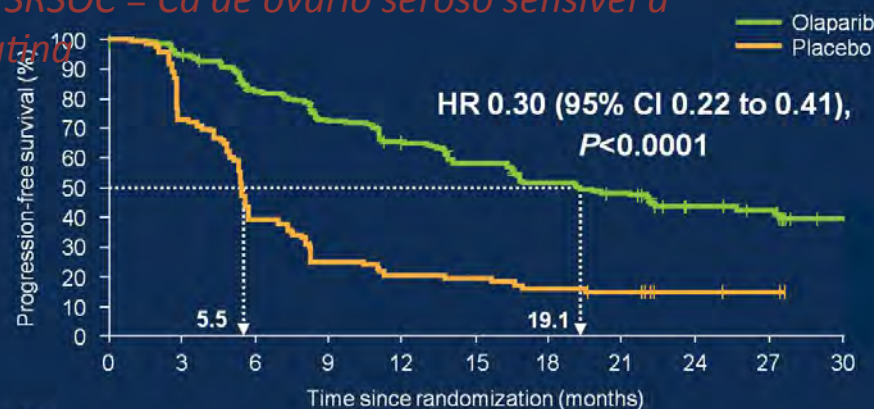
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SOLO 2 trial (Fase III)

SOLO2/ENGOT-Ov21: Phase III trial of olaparib tablet maintenance treatment in patients with PSR SOC and a gBRCAm



* PSRSOC = Ca de ovário seroso sensível a platina



No. at risk

Olaparib	196	182	156	134	118	104	89	82	32	29	3
Placebo	99	70	37	22	18	17	14	12	7	6	0

bid, twice daily; CI, confidence interval; CR, complete response; gBRCAm, germline BRCA mutation; HR, hazard ratio; PFS, progression-free survival; PR, partial response

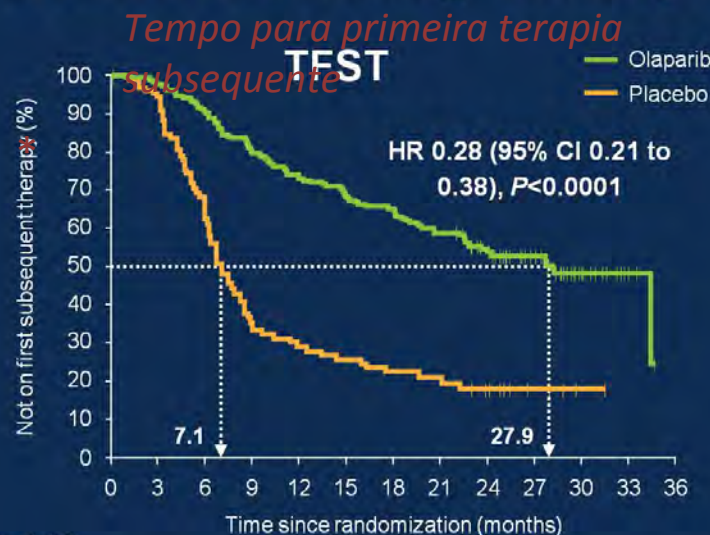
Pujade-Lauraine E *et al.* SGO 2017; abst LBA2

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

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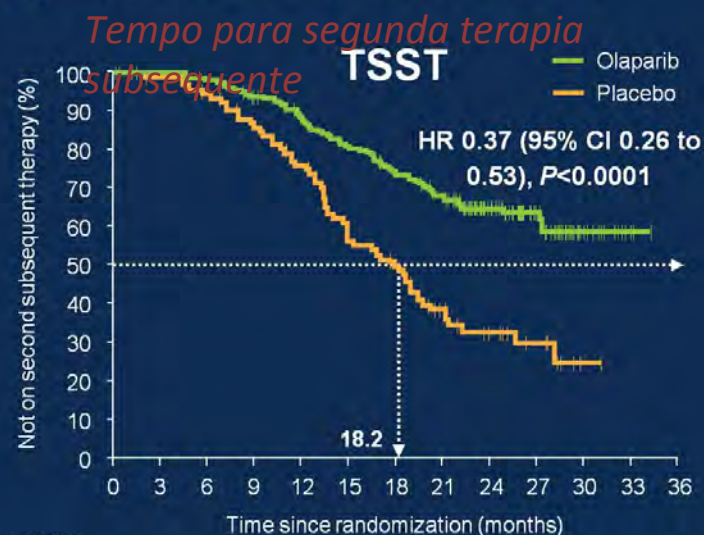
SOLO 2 trial (Fase III)

SOLO2 secondary efficacy endpoints: TFST and TSST



No. at risk

Olaparib	196	190	176	155	139	130	122	107	64	40	16	4	0
Placebo	99	92	65	33	26	23	20	19	11	6	2	0	0



No. at risk

Olaparib	196	194	190	181	169	155	141	123	75	43	17	4	0
Placebo	99	95	90	81	67	51	43	30	17	10	2	0	0

TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

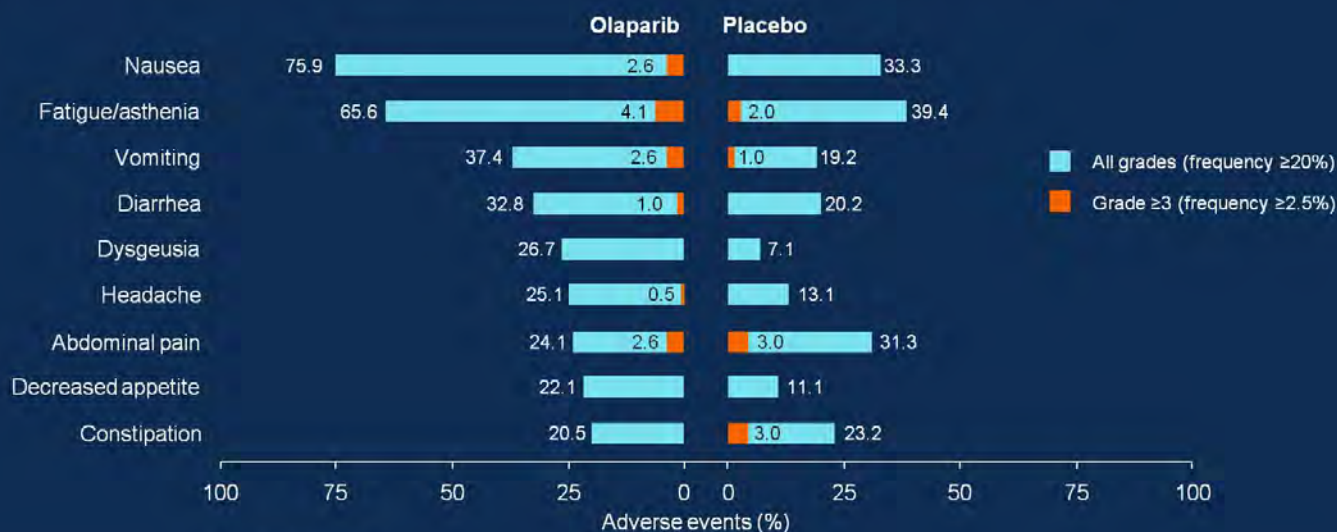
Pujade-Lauraine E *et al.* SGO 2017; abst LBA2

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)

Most common non-hematologic adverse events



Other AEs of interest

Elevated ALT: 10 patients in olaparib group (5.1%) vs 4 patients in placebo group (4.0%)

Elevated AST: 4 patients in olaparib group (2.1%) vs 4 patients in placebo group (4.0%)

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

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○ SOLO 2 (fase III): QoL

PRO hypothesis in SOLO2

Our *a priori* PRO hypothesis was that maintenance therapy with olaparib would not negatively impact on HRQOL versus placebo and would be associated with additional patient-centered benefits to support the prolongation of PFS, the primary endpoint of SOLO2

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

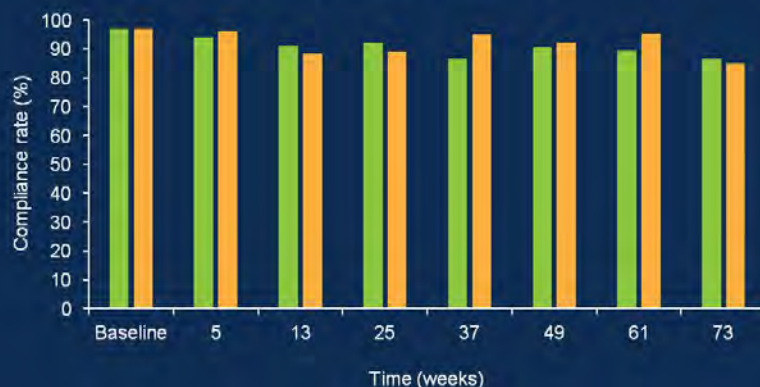
A proposta foi avaliar a Qualidade de vida por meio de questionários validados

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SOLO 2 (fase III): QoL

FACT-O compliance rate

By planned visit:
On study treatment

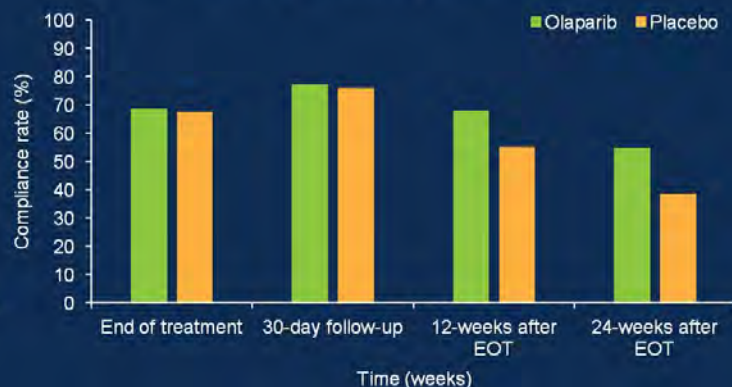


No. of evaluable patients

Olaparib 190 183 172 163 135 125 109 98

Placebo 96 95 84 66 39 24 20 17

By planned visit:
Following disease progression



63

48

51

38

66

43

44

27

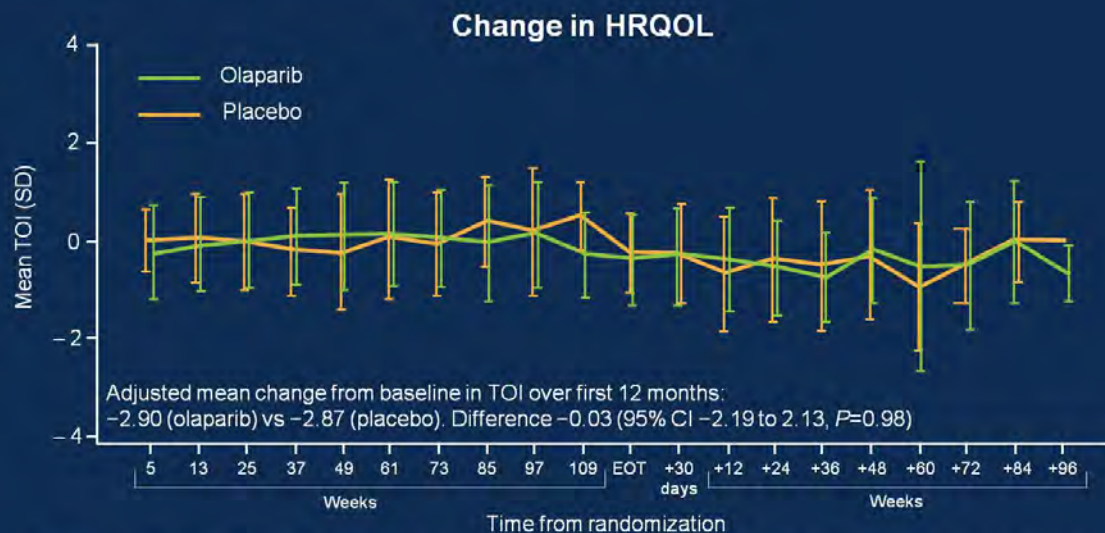
- 1) Os questionários eram aplicados na data de inclusão, no D29 e a cada 12 semanas até progressão. Também 30 dias após a última dose e a cada 12 semanas até o cut-off/primeira análise.
- 2) A adesão ao preenchimento dos dados foi alta até mesmo após progressão.

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SOLO 2 (fase III): QoL

Primary HRQOL analysis: FACT-O TOI

- There was no significant detrimental effect of olaparib versus placebo on HRQOL
- Patients starting maintenance therapy were **relatively well** (mean TOI of 75)*
- Olaparib did not negatively impact on mean TOI score over 12 months



*Scale 0–100; higher scores indicate better HRQOL
 SD, standard deviation

Pujade-Lauraine E *et al.* SGO 2017;abst LBA2

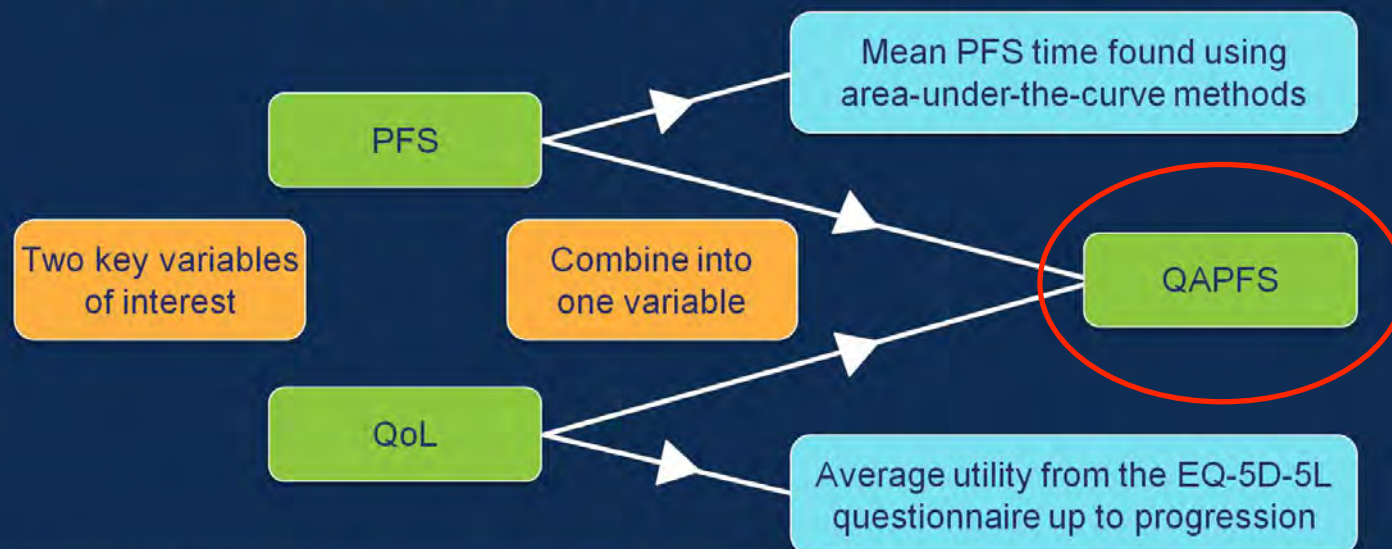
- 1) Pelo que se observa na curva, Olaparibe não impactou negativamente no escore médio de Qualidade de vida (HRQOL)

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SOLO 2 (fase III): QoL

Patient-centered benefits: Secondary analyses

1. Quality-adjusted progression-free survival (QAPFS)



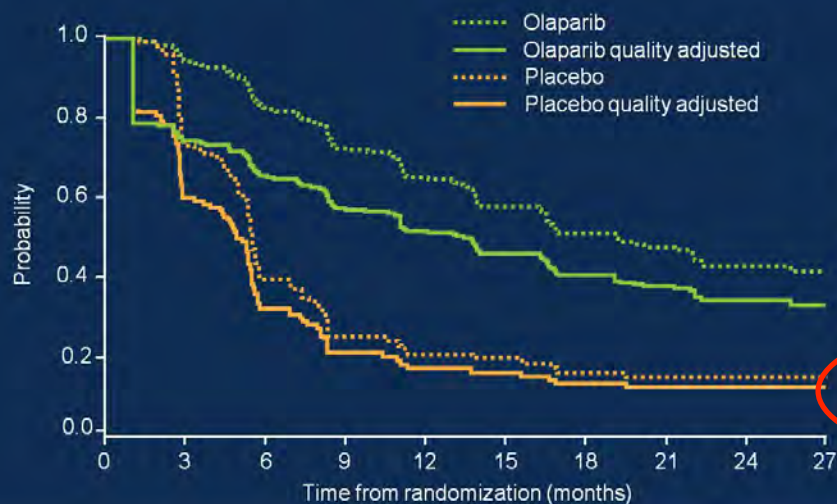
- 1) Entretanto, sozinho, esse dado não permite inferir benefício direto aos pacientes.
- 2) Uma das formas de se tentar melhorar esse dado é fazer uma análise da Qualidade de vida ajustada à sobrevida livre de progressão (QAPFS)

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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

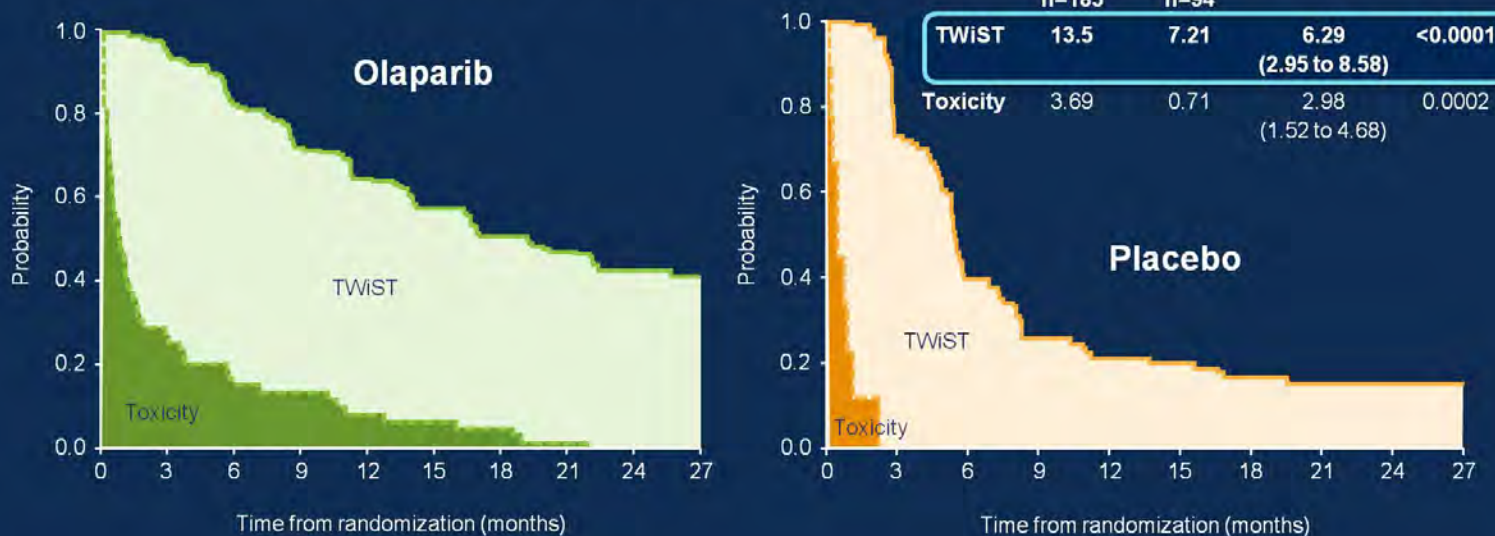
Outra forma de olhar para esses dados é avaliar o Tempo sem sintomas da doença ou toxicidade (TWiST). Essa medida leva em consideração a duração da resposta e a influência de náusea, vômito e fadiga na vida do doente.

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SOLO 2 (fase III): QoL

Results: TWiST

TWiST duration = mean PFS – mean toxicity



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

Conclusions

- In patients with gBRCAm PSR SOC, treatment with olaparib in SOLO2 led to a significant improvement in the primary endpoint of investigator-assessed PFS versus placebo (median increase 13.6 months; HR 0.30 [95% CI 0.22 to 0.41], $P<0.0001$) and in the secondary time-dependent efficacy endpoints (TFST, PFS2, TSST)
- There was no significant detrimental effect of olaparib versus placebo on HRQOL (primary HRQOL analysis, FACT-O TOI scores)
- Despite the toxicity associated with olaparib versus placebo, significant 'patient-centered benefits' of olaparib versus placebo were observed
 - Significantly longer quality-adjusted PFS
 - Significantly longer time without symptoms of disease or treatment toxicity

PFS2, time to second disease progression

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

Phase II randomized trial of neoadjuvant chemotherapy with or without bevacizumab in advanced epithelial ovarian cancer (GEICO 1205/NOVA trial)



Y Garcia Garcia¹, A De Juan², C Mendiola³, M Pilar Barretina-Ginesta⁴, A Prat⁵, A Santaballa⁶, I Bover⁷, M Gil-Martin⁸, A Manzano⁹, M Jesus Rubio¹⁰, M Romeo¹¹, C Arqueros¹², E Garcia Martinez¹³, A Gonzalez-Martin¹⁴

¹Hospital Parc Tauli Sabadell, Sabadell; ²Hospital Marques de Valdecilla, Santander; ³Hospital Universitario 12 De Octubre, Madrid; ⁴Catalan Institute of Oncology-IDIBGi, Girona; ⁵Hospital Clínic i Provincial de Barcelona, Barcelona; ⁶Hospital Universitari i Politècnic La Fe, Valencia; ⁷Hospital Son Llàtzer, Palma De Mallorca; ⁸Institut Català d'Oncologia-IDIBELL, L'Hospitalet, Barcelona; ⁹Hospital Universitario Clínico San Carlos, Madrid; ¹⁰Hospital Reina Sofia, Córdoba; ¹¹Catalan Institute of Oncology, Badalona; ¹²Hospital de la Santa Creu i Sant Pau, Barcelona; ¹³Hospital G Universitario Morales Meseguer, UMU, IMIB-Arrixaca, Murcia; ¹⁴MD Anderson Cancer Center Madrid, Madrid

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NOVA = Neoadjuvant therapy in advanced Ovarian cancer with AVastin
ClinicalTrials.gov NCT01847677

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NOVA trial (fase II)

Rationale for neoadjuvant BEV

- In advanced eOC, standard therapy is cytoreductive surgery and CP ($\pm$ 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 progression⁶
- 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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¹Karam Ann Oncol 2017; ²Vergote NEJM 2010; ³Kehoe Lancet 2015; ⁴Burger NEJM 2011; ⁵Perren NEJM 2011; ⁶Oza Lancet Oncol 2015

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NOVA trial (fase II)

Well-balanced baseline characteristics

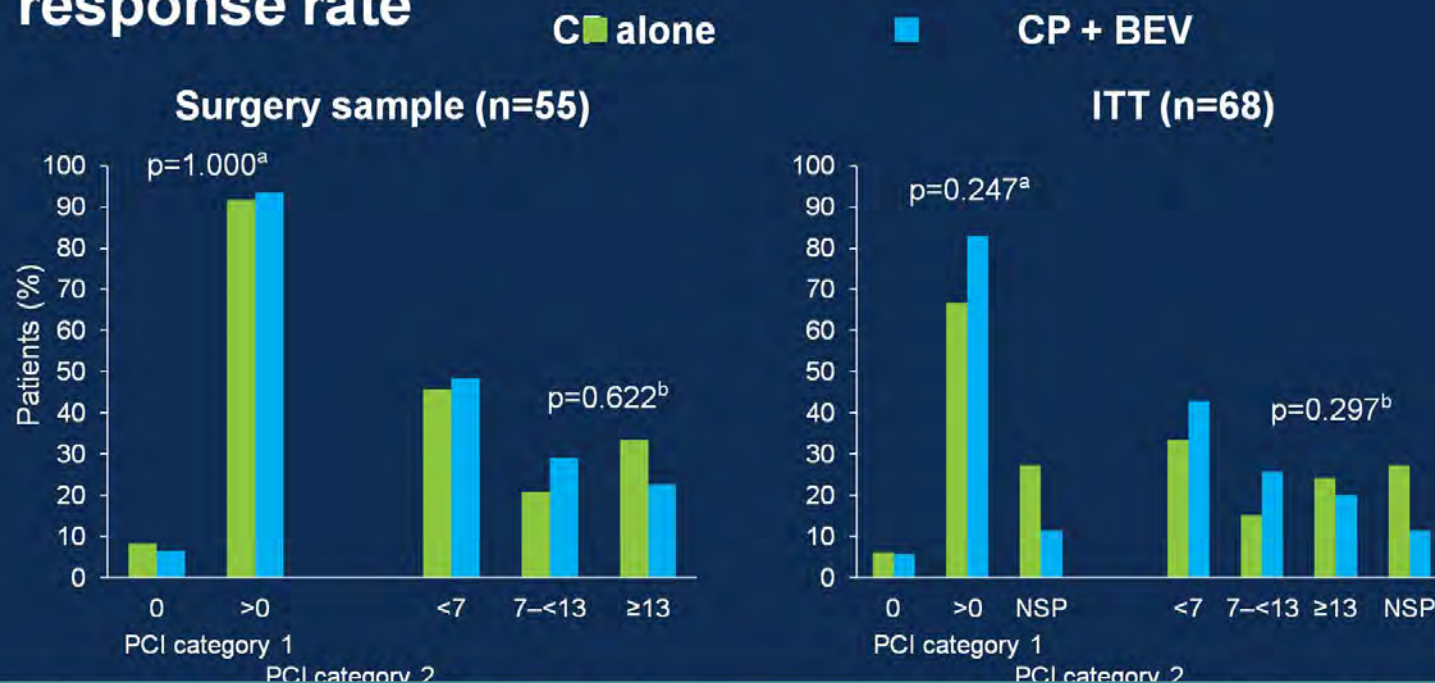
Characteristic		CP alone (n=33)	CP + BEV (n=35)
Median age, years (range)		57 (36–82)	63 (33–78)
ECOG PS, n (%)	0	5 (15)	8 (23)
	1	21 (64)	24 (69)
	2	7 (21)	3 (9)
Origin of cancer, n (%)	Ovary	25 (76)	31 (89)
	Primary peritoneal	7 (21)	4 (11)
	Fallopian tube	1 (3)	0
FIGO stage, n (%)	IIIC	22 (67)	23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

Primary endpoint: Complete macroscopic response rate



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)

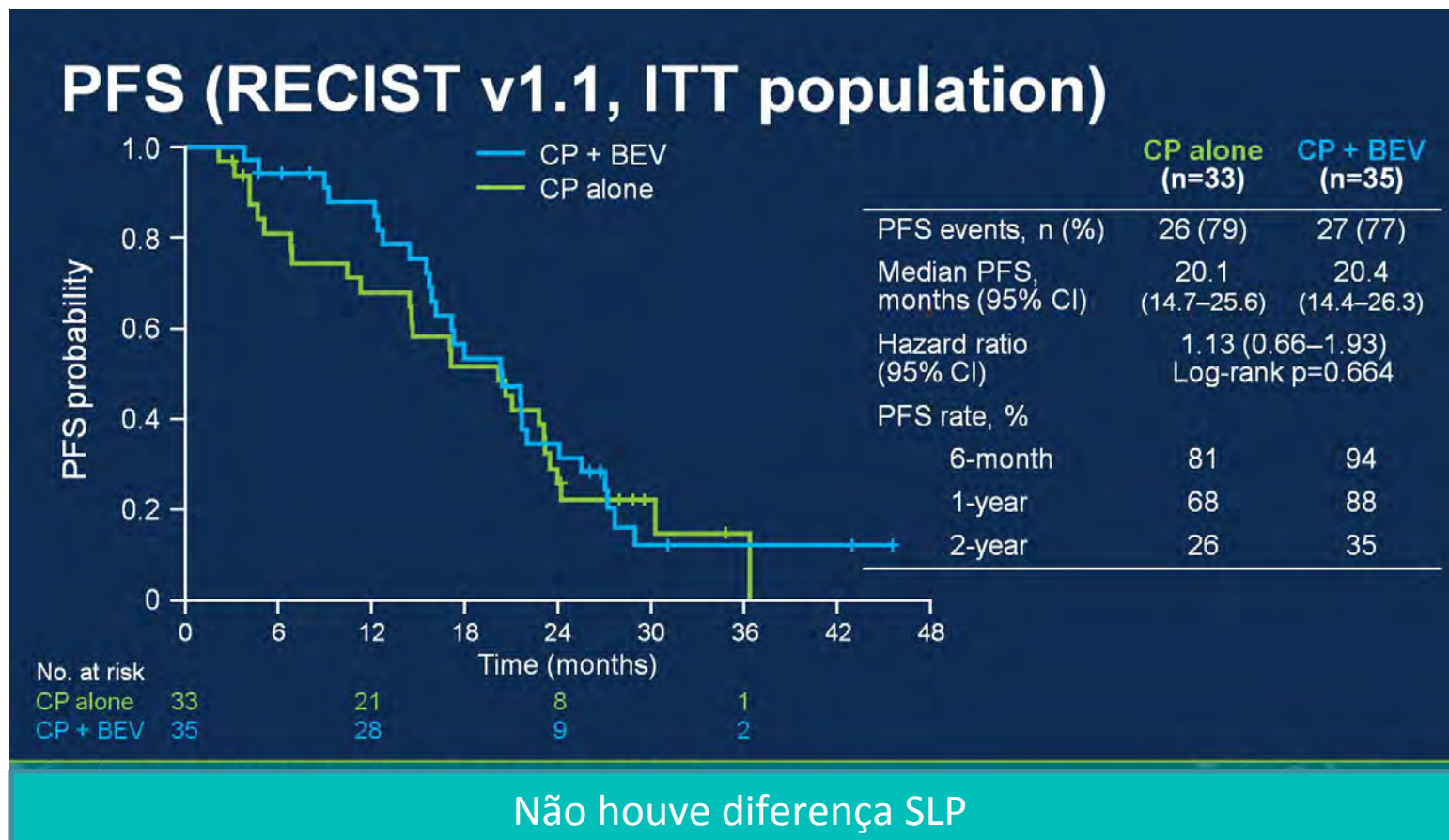
^aChi-squared test. ^bFisher's exact test

^cSurgery 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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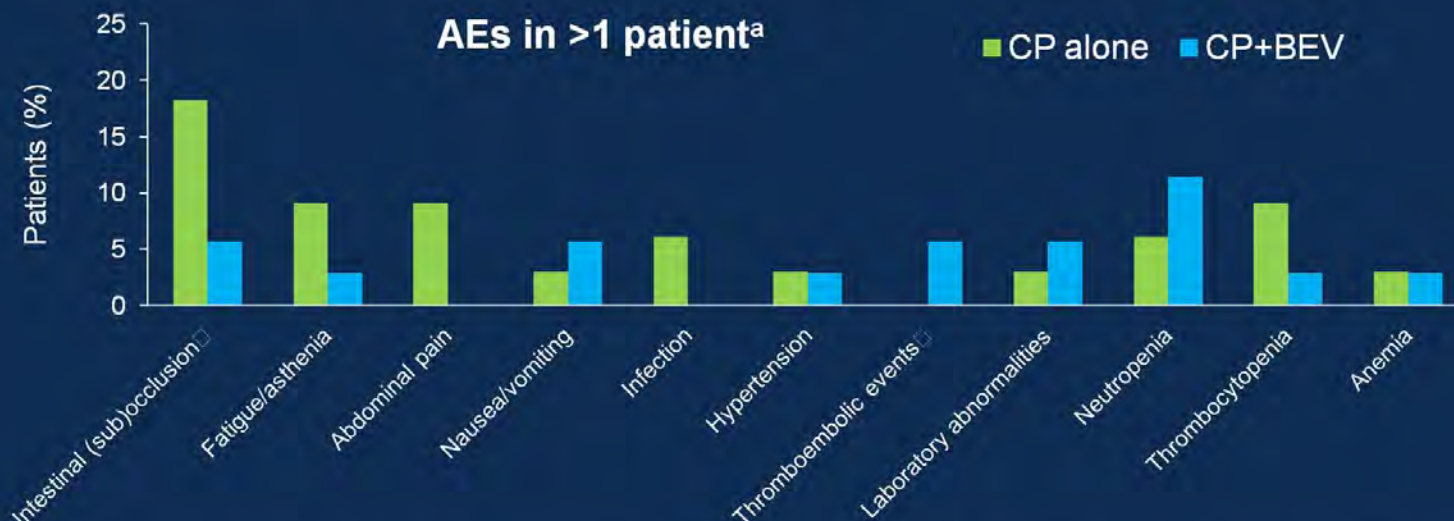
NOVA trial (fase II)



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NOVA trial (fase II)

Grade ≥ 3 AEs during NACT



^aOne additional case each of: allergy, anxiety/depression, arthromyalgia, bilateral hydronephrosis, pain in limbs, dyspnea, and neurotoxicity (CP-alone arm) and ascites and leukopenia (CP + BEV arm). ^b(Partial) bowel/intestinal obstruction, intestinal (sub)occlusion. ^cDeep vein thrombosis, pulmonary embolism
AE = adverse event

Padrão de distribuição de EVENTOS ADVERSOS > G3

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NOVA trial (fase II)

Conclusions

- The addition of BEV to NACT in patients initially considered to be unresectable did not improve the complete macroscopic response rate at IDS (primary endpoint), which was <10% in both arms
- Although NACT + BEV improved surgical feasibility at IDS, neither the rate of optimal cytoreduction nor PFS was improved with 3–4 additional preoperative cycles of BEV
- Adding BEV to NACT did not increase the overall rate of grade ≥ 3 AEs
- Our results support the early integration of BEV in carefully selected high-risk patients requiring NACT for unresectable disease at diagnosis

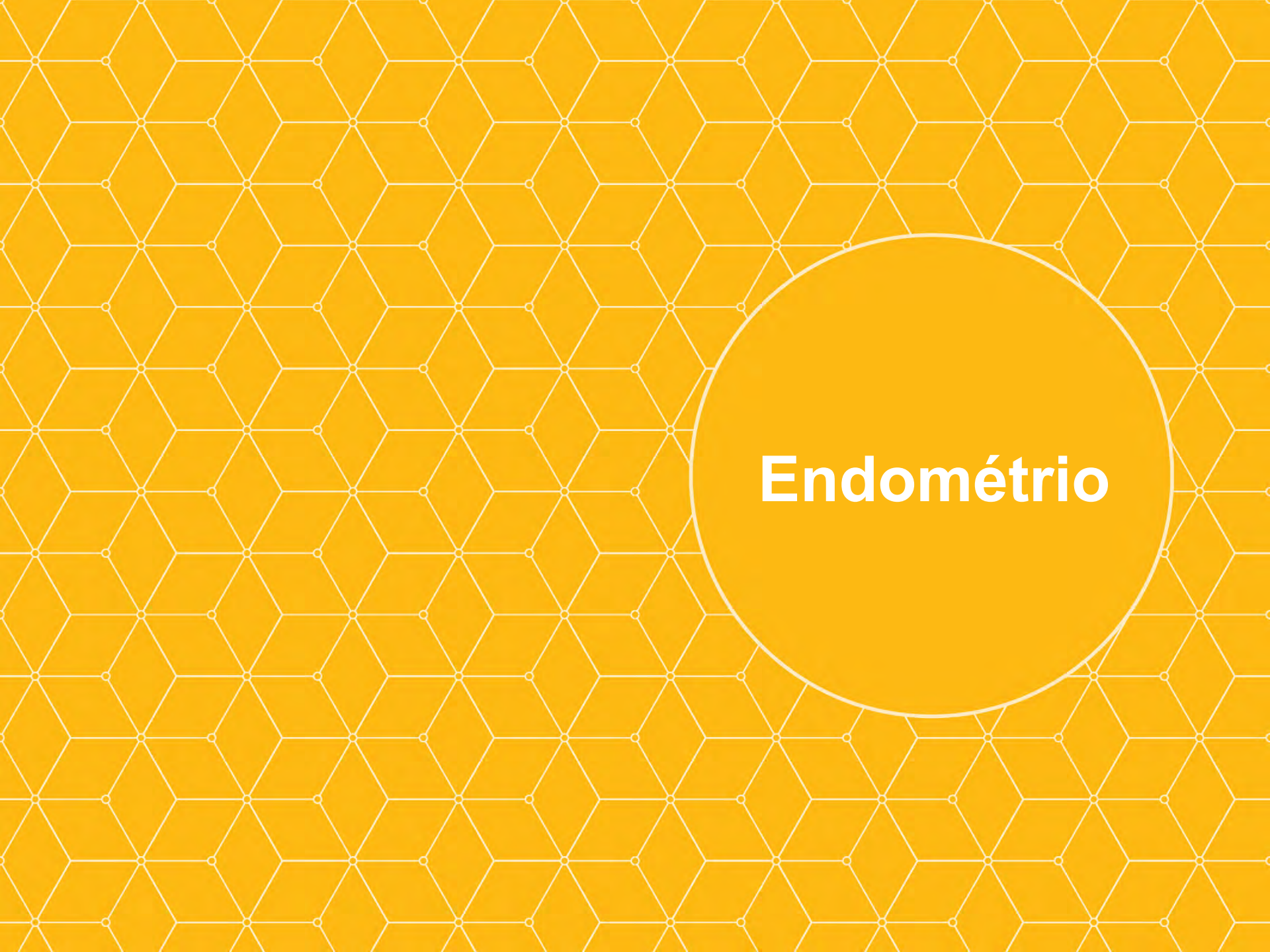
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¹Rouzier EJC 2017

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Endométrio

Resultados finais do PORTEC-3



Final results of the PORTEC-3 trial

ASCO Annual meeting 2017

PORTEC-3 international collaborators



Stephanie de Boer

Department of Radiation Oncology

Leiden University Medical Center, the Netherlands



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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

PORTEC-3 results

Susumu GynOnc 2008; Maggi BJC 2006; Greven GynOnc 2006; Hogberg EJC 2010

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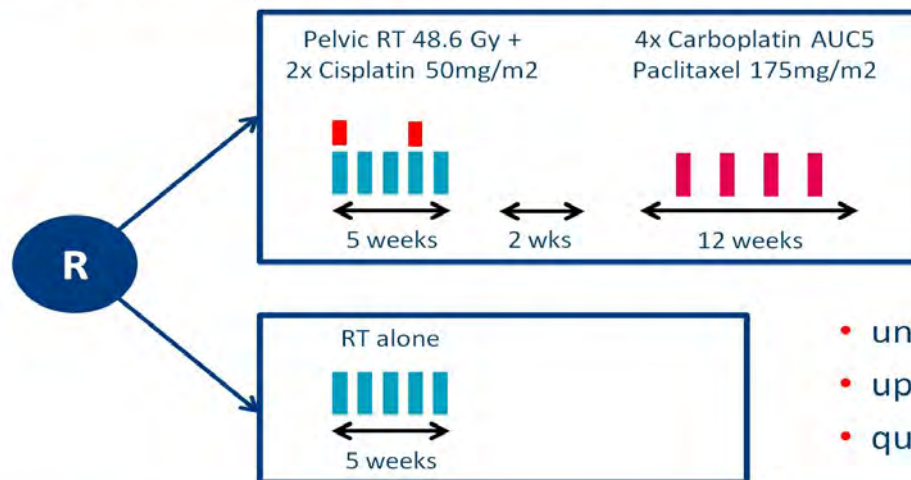


PORTEC-3

PORTEC-3 trial design



➤ High risk Endometrial Cancer (HREC)



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

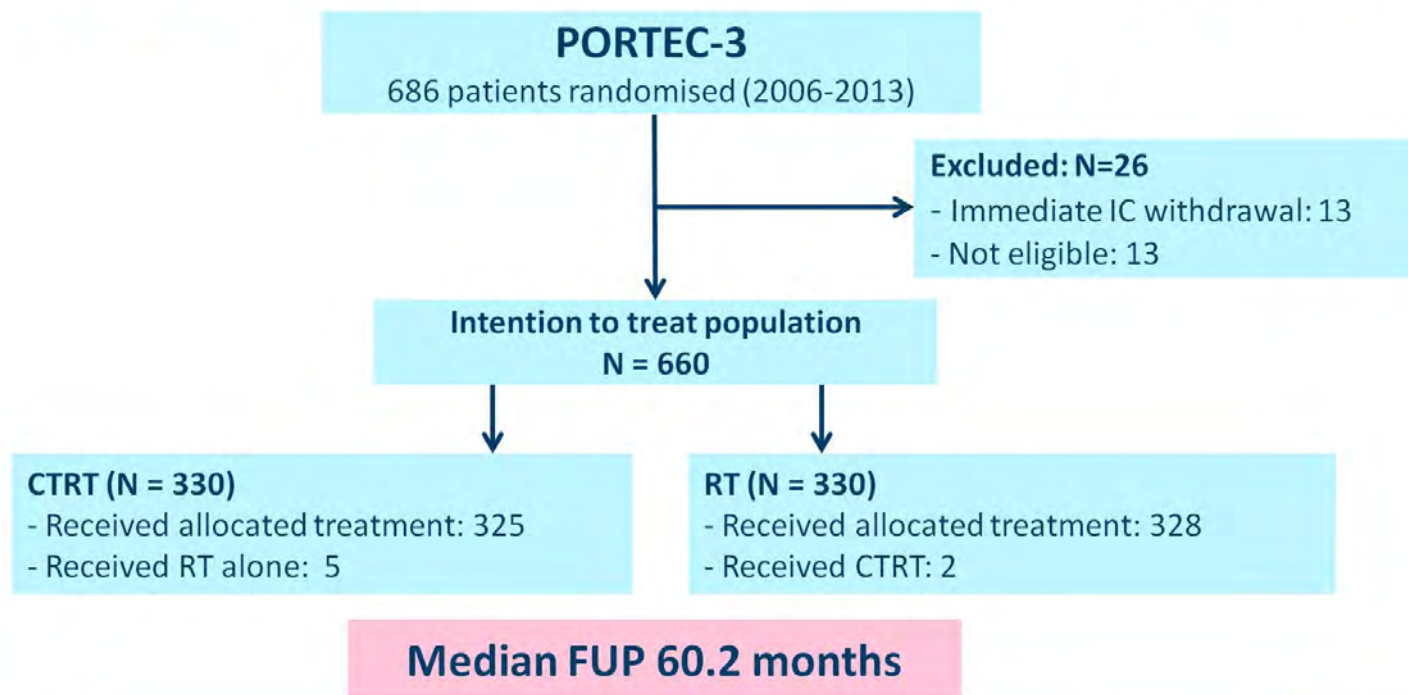
Inclusion criteria

- 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

CONSORT diagram



PORTEC-3 results

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Patient characteristics



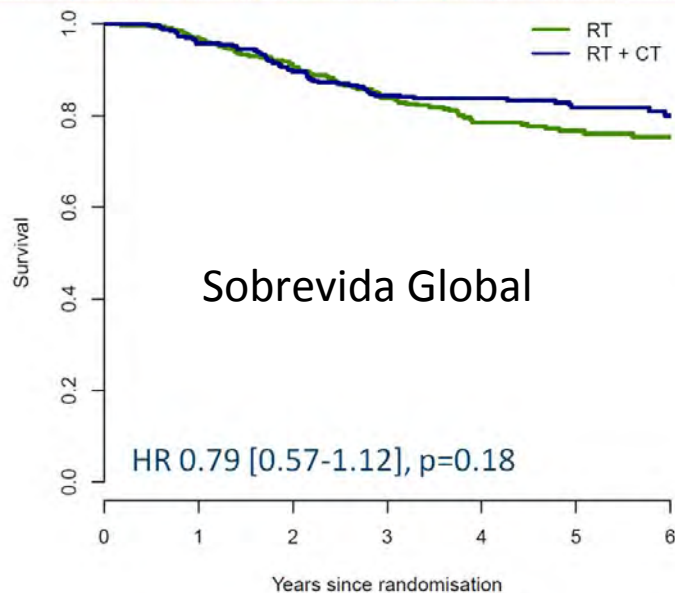
Patient characteristics	RT alone	CTRT	Tumour characteristics	RT alone	CTRT
Age (yr)			Histology		
Median	62.0	62.4	Endometrioid grade 1-2	39.7%	38.5%
IQ Range	55.8-68.2	56.5-67.9	Endometrioid grade 3	32.1%	32.4%
			Serous/ clear cell/ other	28.2%	29.1%
WHO PS (%)			LVSI		
0-1	98.5%	98.5%	Yes	58.2%	59.7%
2	1.5%	1.5%	No	41.8%	40.3%
Comorbidities (%)			Stage (%)		
Diabetes	10.9%	13.7%	I 30% I e 25% II	29.4%	29.7%
Hypertension	31.6%	35.2%	II	27.3%	24.2%
Cardiovascular	6.1%	8.9%	III	43.3%	46.1%

PORTEC-3 results

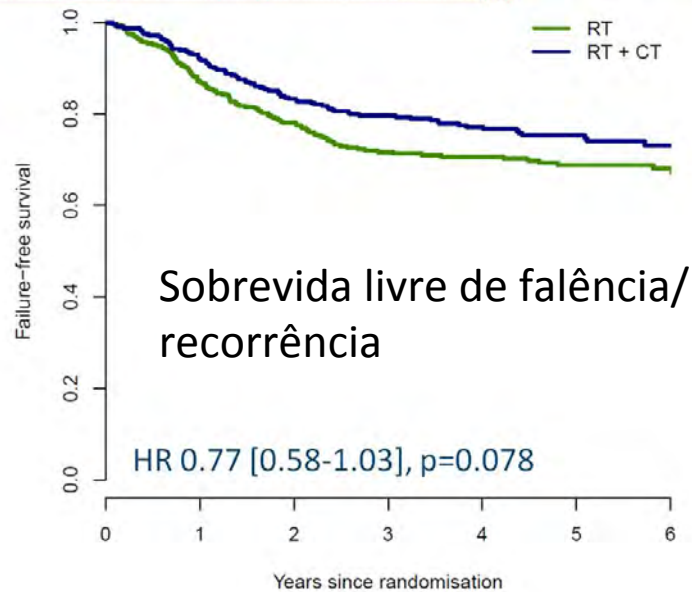
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Survival (OS and FFS)



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



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



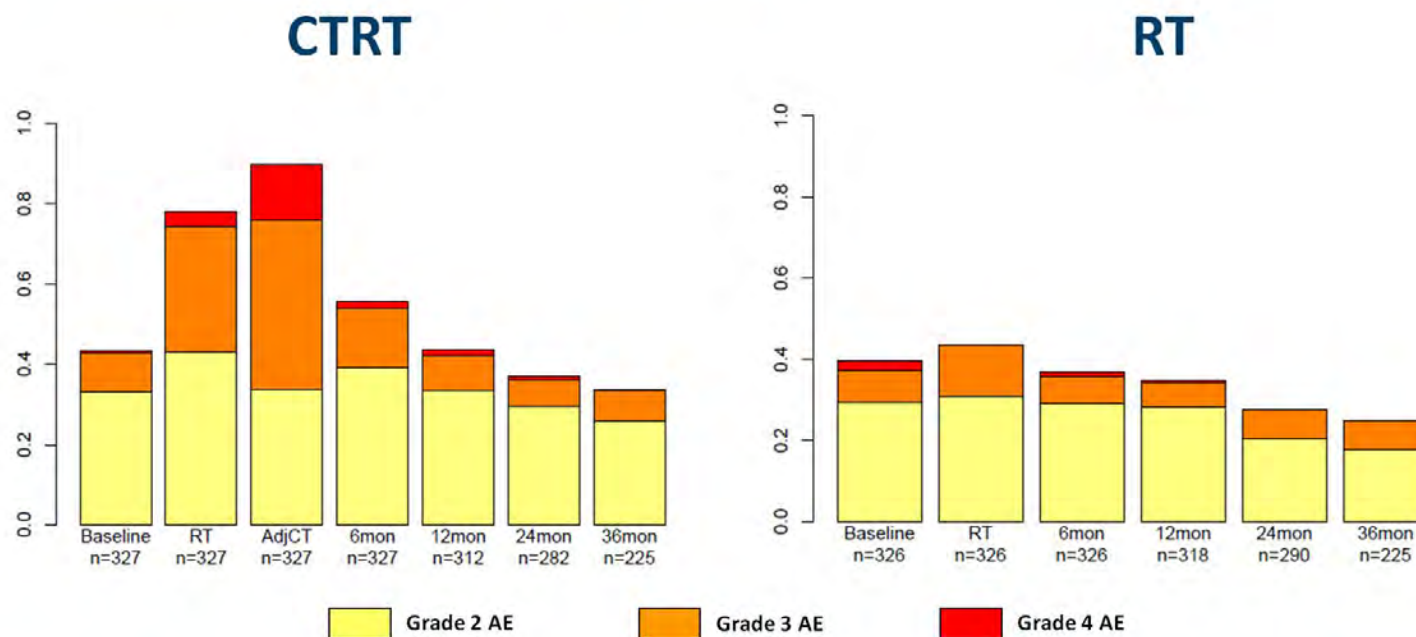
Patients with stage III EC:

- 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, $p = 0.114$]

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

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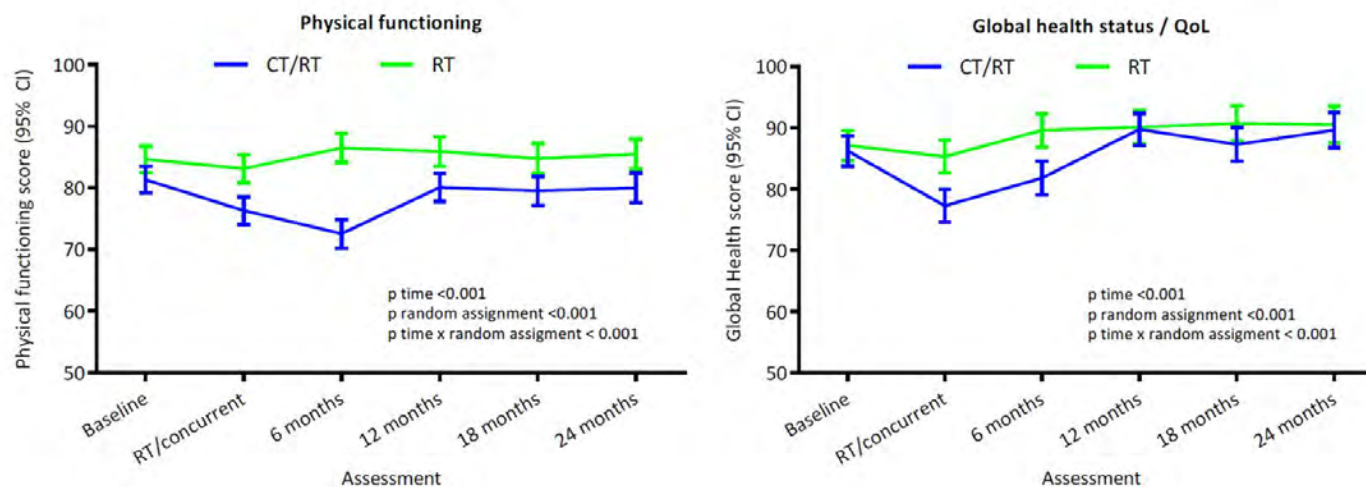
Adverse events (CTCAE v3.0)



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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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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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

PORTEC-3 results

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

A Randomized Phase III Trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Locally Advanced Endometrial Carcinoma *A Gynecology Oncology Group/NRG Oncology Study*

Daniela Matei, Virginia Filiaci, Marcus Randall, David Mutch, Margaret Steinhoff, Paul DiSilvestro, Katherine M. Moxley, Byoung Kim, Matthew A. Powell, David M. O'Malley, Nicola M. Spirtos, Krishnanu S. Tewari, Edward Richards, John Nakayama, David Miller

Northwestern University; NRG Oncology SDMC, Buffalo, NY; University of Kentucky, Women and Infants Hospital in Rhode Island, University of Oklahoma Health Sciences Center, Samsung Medical Center, Sungkyunkwan University School of Medicine.; Washington University School of Medicine in St. Louis.; The Ohio State University College of Medicine; Womens' Cancer Center; University of California Irvine Medical Center, Lewis Cancer and Research Pavilion at St. Joseph's/Candler, University Hospital; The University of Texas Southwestern Medical Center

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Presented by: Daniela Matei, MD

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Research Hypothesis

Combined systemic chemotherapy and tumor volume directed radiotherapy (C-RT) improves recurrence-free survival and overall survival compared to systemic chemotherapy alone (CT) in patients with optimally debulked stage III/IVA EC.

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Study Schema

Objetivo primário: SLR

Objetivos secundários: SG,
Segurança, QoL

TAH/BSO, Pelvic and para-aortic
lymph node sampling optional

Eligibility:

Surgical Stage III or IVA EC (FIGO 2009)
Stage I or II clear cell or serous EC + cytology
GOG Performance Status of 0-2
Adequate organ function

Ineligible Patients

Carcinosarcoma
Recurrent EC
Residual tumor after surgery > 2 cm

Randomization 1:1

Regimen 1: C-RT (n=407)

Cisplatin 50 mg/m² IV Days 1 and 29 plus Volume-directed
radiation therapy (45Gy+/- brachytherapy)
followed by
Carboplatin AUC 5* plus Paclitaxel 175 mg/m² q 21 days
for 4 cycles with G-CSF support

Regimen 2: CT (N=406)

Carboplatin AUC 6 plus Paclitaxel 175 mg/m²
q 21 days for 6 cycles

Stratification:

Age >/< 65
Gross residual disease

CT scans q 6months X 2 years, q 12 months X 3 years

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Patient Characteristics

Characteristic	C-RT (N=370)		CT (N=366)	
	N	%	N	%
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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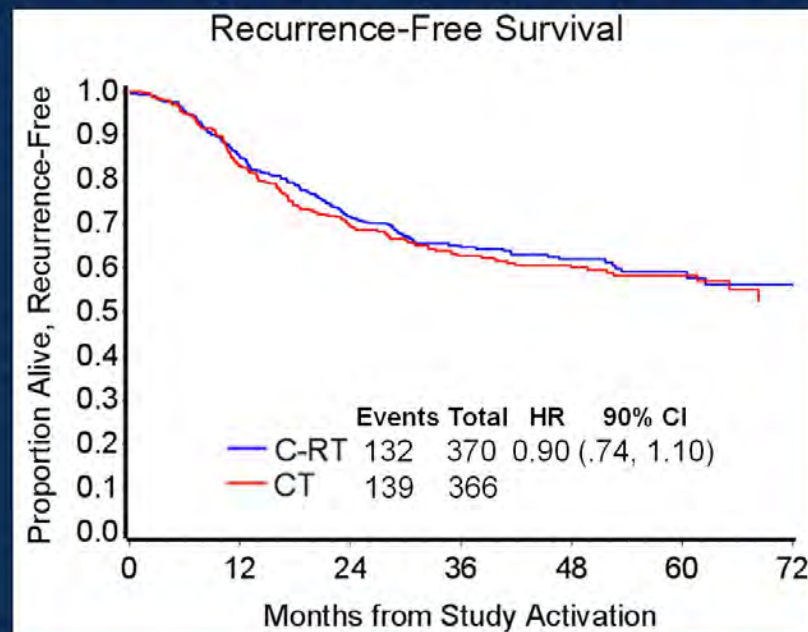
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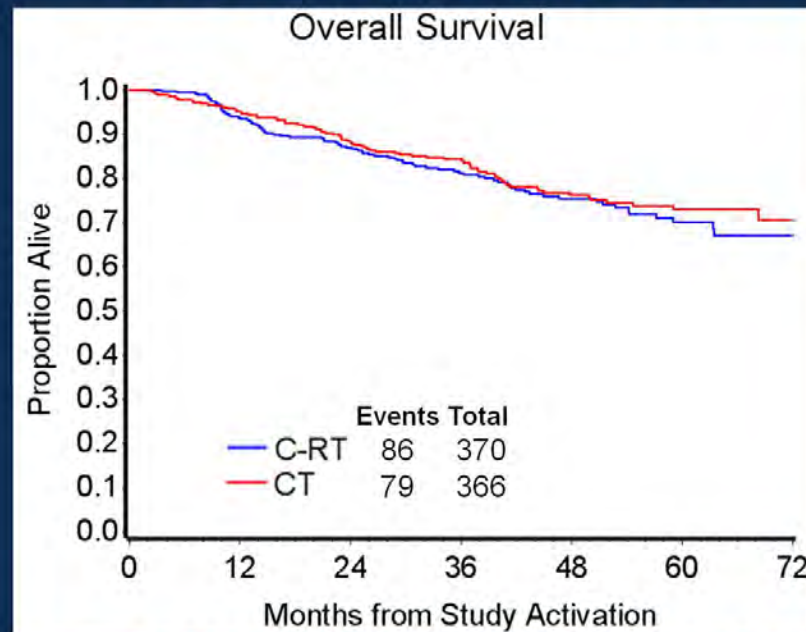
Recurrence-Free Survival



O estudo falhou em comprovar seu Objetivo primário.

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Overall Survival



5 year OS estimates
C-RT: 70%
CT: 73%

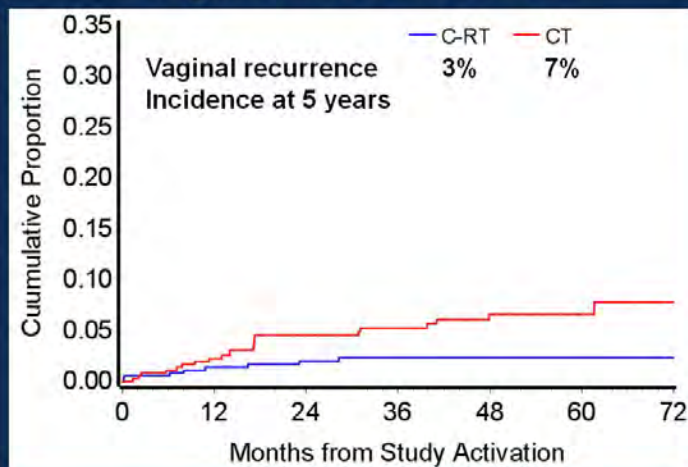
Data cut-off 03/09/2017 Data not mature for final analysis

Também não houve vantagem em SG

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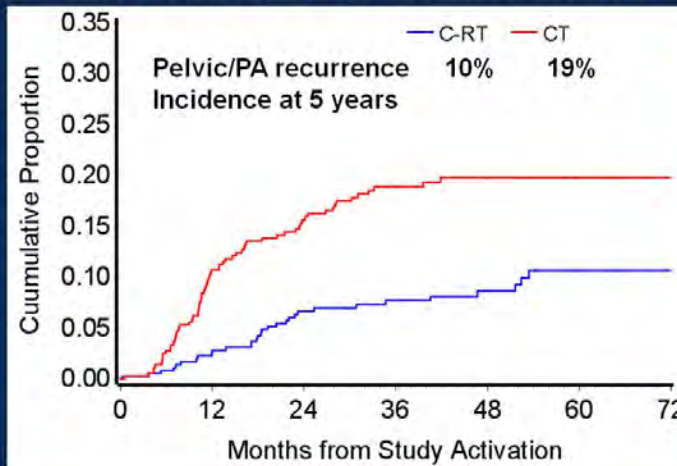
Cumulative Incidence of Recurrence

Vaginal Recurrence



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

Pelvic and PA Recurrence



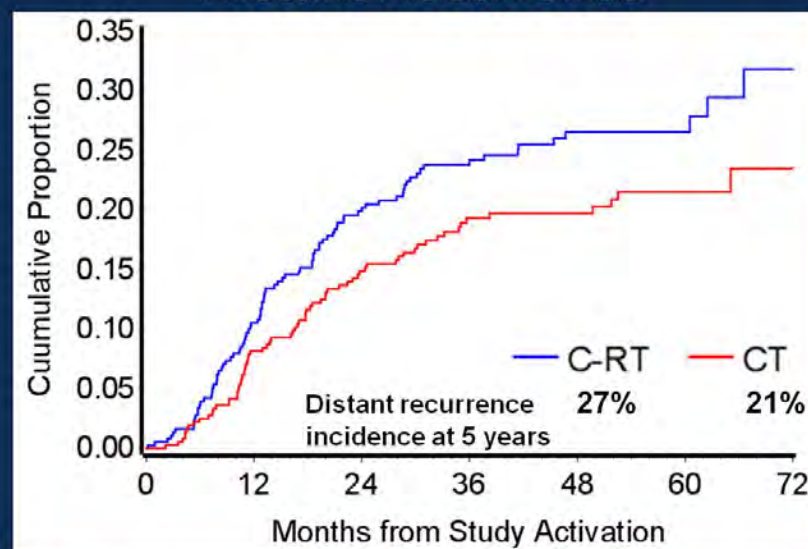
C-RT vs. CT : HR=0.43 (CI: 0.28-0.66)

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

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Cumulative Incidence of Recurrence

Distant Recurrence



C-RT vs. CT : HR=1.36 (CI: 1.00-1.86)

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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Conclusions

- Chemo-RT did not improve RFS compared to chemotherapy (HR=0.9, CI 0.74-1.1).
- Acute toxicities for chemo-RT and chemotherapy were similar.
- 75% patients completed study therapy in C-RT arm compared to 85% patients in CT arm.
- Chemo-RT reduced the incidence of vaginal, pelvic and para-aortic recurrences compared to CT.
- Distant recurrences were more common with C-RT vs. CT.
- Survival and QOL endpoints will be reported in the future.

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

A randomized phase III trial of docetaxel plus cisplatin or paclitaxel plus carboplatin compared with doxorubicin plus cisplatin as adjuvant chemotherapy for endometrial cancer at high risk of recurrence: Japanese Gynecologic Oncology Group Study (JGOG2043)

Nomura H, Aoki D, Michimae H, Mizuno M, Nakai H, Arai M, Sasagawa M, Ushijima K, Sugiyama T, Saito M, Tokunaga H, Omatsu K, Nakanishi T, Watanabe Y, Saito T, Yaegashi N

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Rationale for Taxane/Platinum Regimens



- Doxorubicin has been the key drug and doxorubicin plus cisplatin (AP) has been the standard regimen for endometrial cancer.
- Recently, the superiority of a paclitaxel plus platinum regimen was demonstrated (GOG177², GOG209³).
- JGOG conducted a randomized phase II trial for advanced or recurrent endometrial cancer (JGOG2041⁴), which showed adequate efficacies of the taxane plus platinum regimens (response rate: 48.3-60.0%).

2. J Clin Oncol, 2004;22:2159-66 3. Gynecol Oncol, 2012;125:771-3 4. Ann Oncol, 2011;22:636-42

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Objective of Trial



In adjuvant chemotherapy for endometrial cancer patients at a high risk of recurrence* after surgery,

to evaluate the clinical benefit of the taxane plus platinum regimens including **docetaxel plus cisplatin (DP)** or **paclitaxel plus carboplatin (TC)** as compared with **doxorubicin plus cisplatin (AP)**.

*high risk of recurrence

- stage I, II with G2/G3 and a myometrial invasion >1/2
- stage III
- stage IV with no metastatic lesions beyond the abdominal cavity

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Trial Design



Endometrial cancer at a high risk of recurrence

- stage I, II with G2/G3 and a myometrial invasion >1/2
- stage III
- stage IV with no metastatic lesions beyond the abdominal cavity

Adjustment factors:

- FIGO surgical stage (I, II vs III, IV)
- histologic grade (G1, G2 vs G3, others)

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Standard arm: AP

A: Doxorubicin 60 mg/m², I.V., day 1
P: Cisplatin 50 mg/m², I.V., day 1
every 21 days for 6 cycles

Experimental arm 1: DP

D: Docetaxel 70 mg/m², I.V., day 1
P: Cisplatin 60 mg/m², I.V., day 1
every 21 days for 6 cycles

Experimental arm 2: TC

T: Paclitaxel 180 mg/m², I.V., day 1
C: Carboplatin AUC 6, I.V., day 1
every 21 days for 6 cycles

- **Primary endpoint:**
 - Overall survival
- **Secondary endpoints:**
 - Progression-free survival
 - Quality of life as measured by EORTC QLQ-C30, OV 28
 - Number of resected lymph nodes

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Patient Characteristics (1)



Characteristics		AP (N=263)	DP (N=263)	TC (N=262)
		No. of patients (%)	No. of patients (%)	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)

Treatment Tolerability



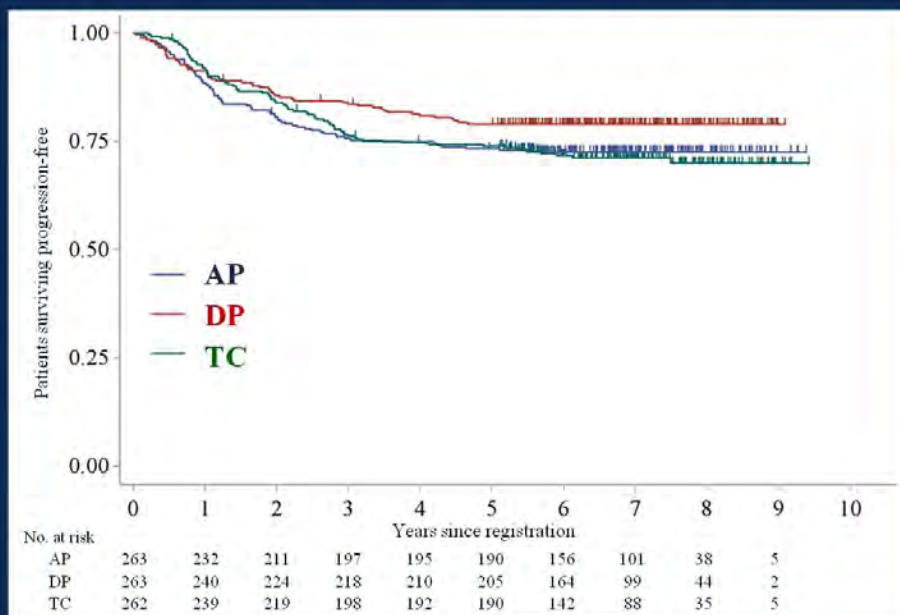
Tolerability		AP (N=263)	DP (N=263)	TC (N=262)
		No. of patients (%)	No. of patients (%)	No. of patients (%)
Completed protocol treatment		210 (79.8)	218 (82.9)	199 (76.0)
Discontinued due to:	Progressive disease / Deaths	5 (1.9)	6 (2.3)	3 (1.1)
	Adverse events (AEs)	17 (6.5)	15 (5.7)	32 (12.2)
	Patients 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%	D: 92.6%	T: 86.4%
		P: 88.5%	P: 92.9%	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)



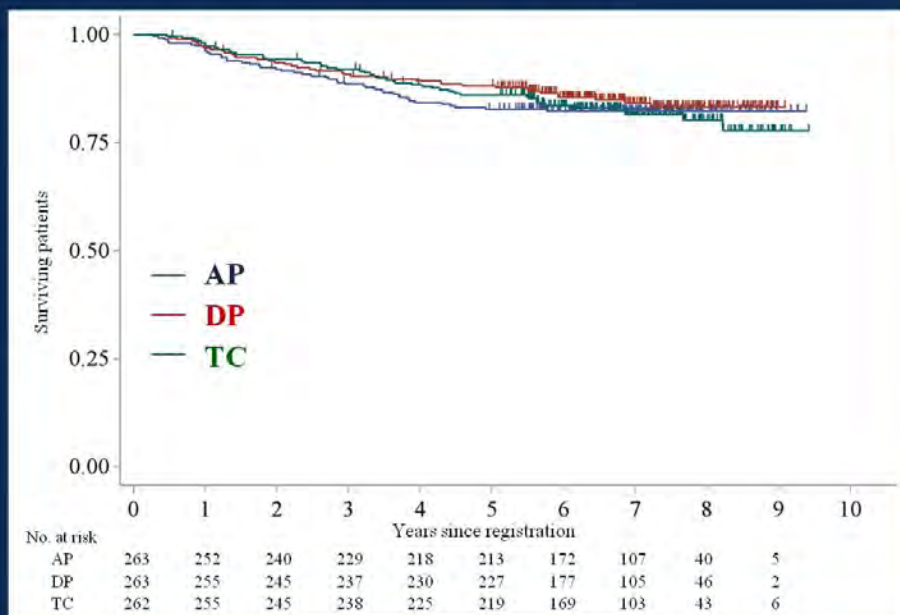
Arm	N	Events	5-yr PFS	Log-rank test
AP	263	72	74.5%	P=0.1246
DP	263	55	80.5%	
TC	262	75	74.3%	

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)



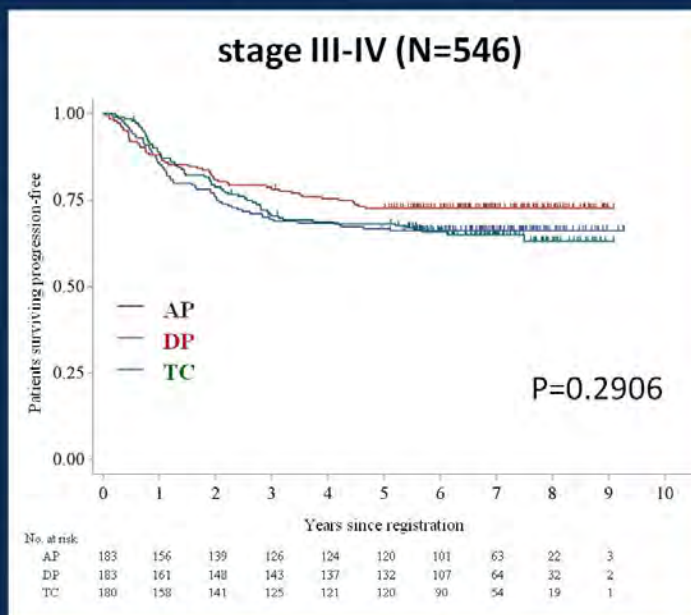
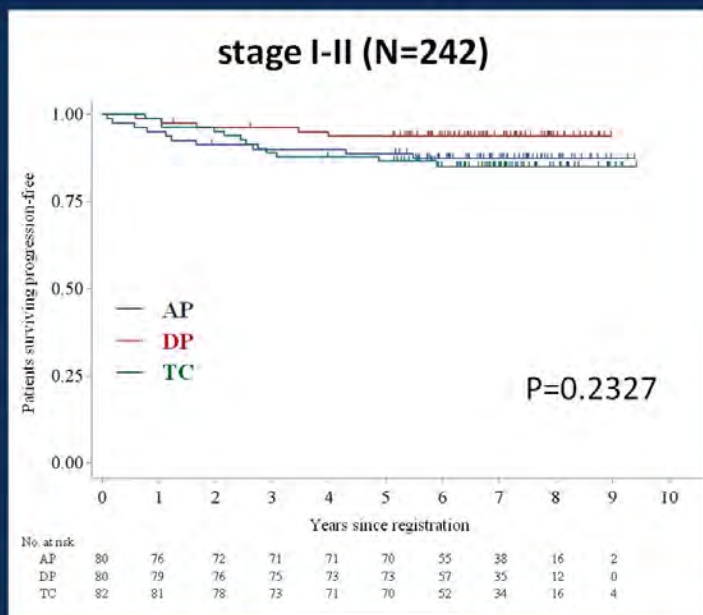
Arm	N	Events	5-yr OS	Log-rank test
AP	263	46	83.9%	P=0.6734
DP	263	40	88.9%	
TC	262	47	88.0%	

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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Conclusions



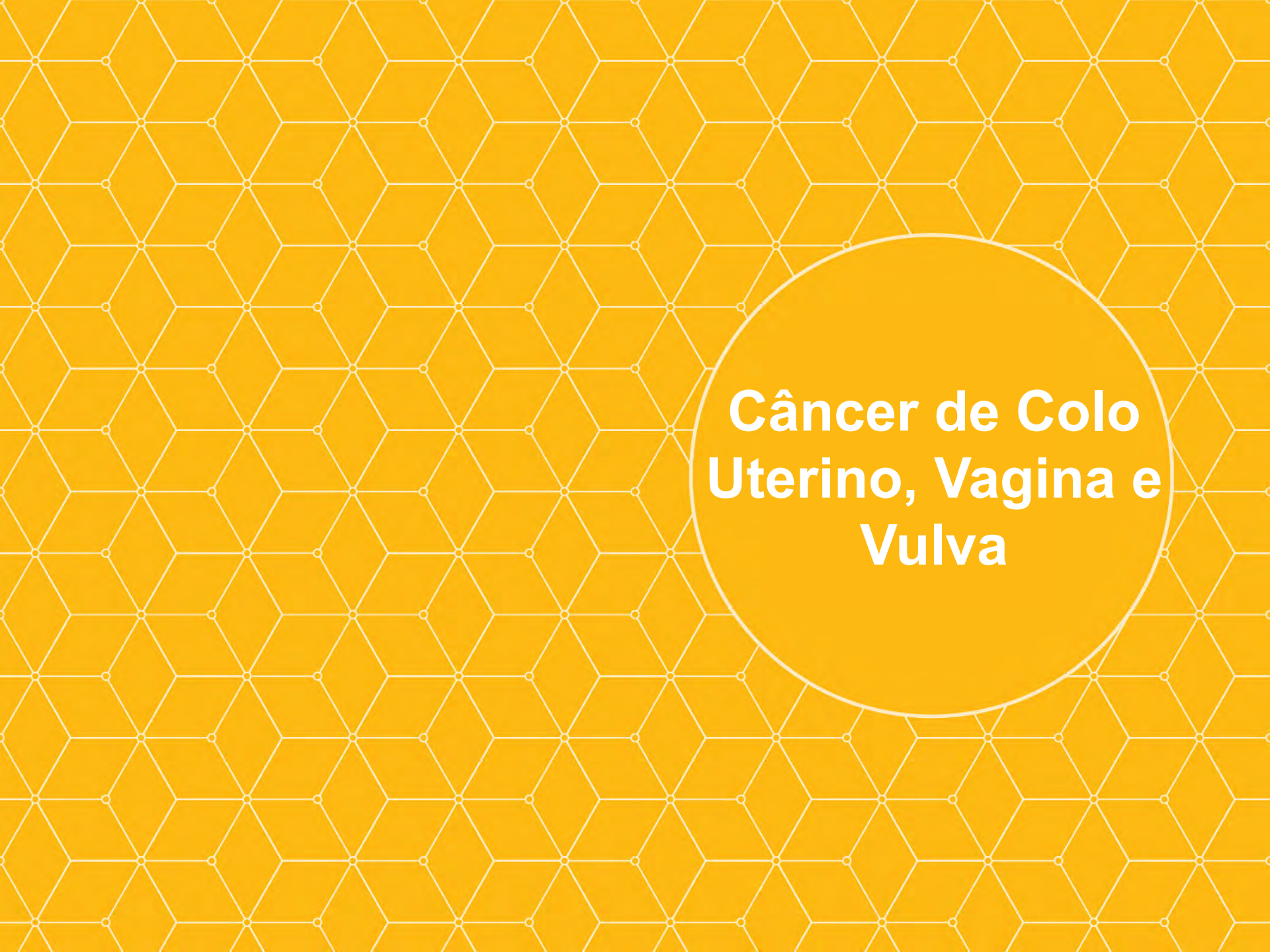
- In this trial, a survival benefit was not observed in DP (docetaxel plus cisplatin) or TC (paclitaxel plus carboplatin) compared with AP (doxorubicin plus cisplatin) as adjuvant chemotherapy for endometrial cancer at a high risk of recurrence.
- Since each regimen showed adequate tolerability, the taxane plus platinum regimens may be a reasonable alternative to AP. And DP is worth considering as a future treatment arm.

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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 María 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. Topalian¹²

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

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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 cancers²
 - 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 cancer⁷
- 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 Hematol 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.

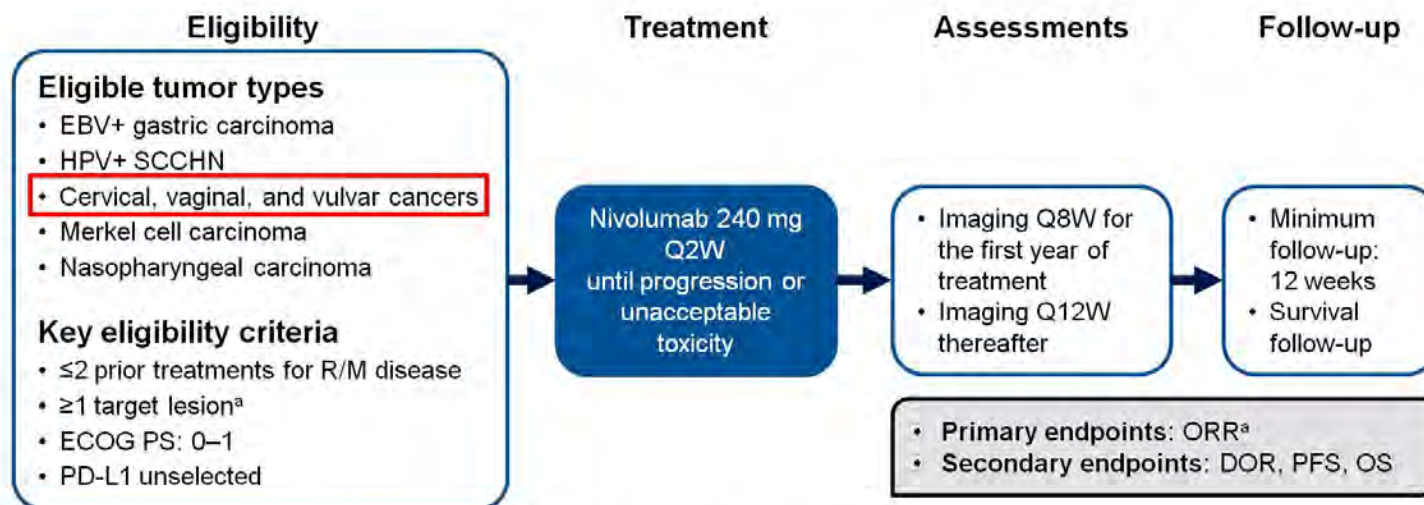
O HPV é capaz de promover *upregulation* do PD-L1 em células tumorais.

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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



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

^aPer 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)

^aECOG PS not reported in 1 patient at time of data cutoff; ^bPer local site testing

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CheckMate 358

Best Overall Response

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

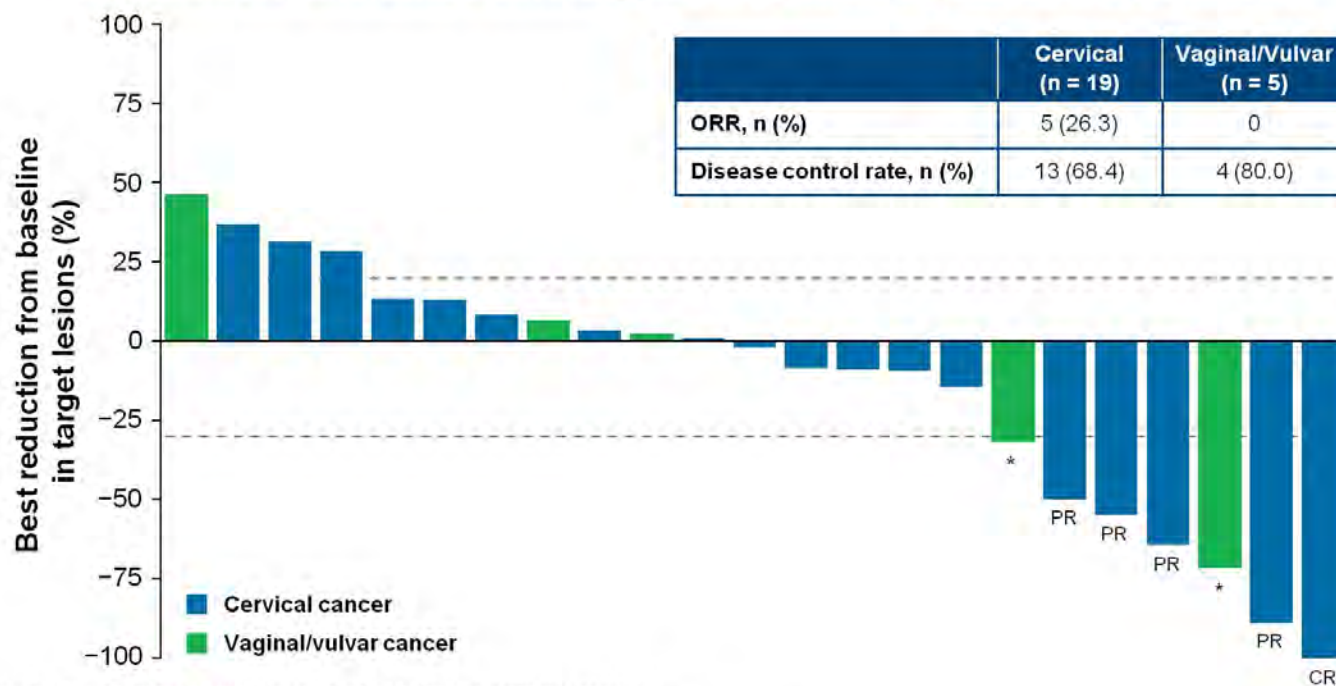
	All patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)
Best overall response, n (%)			
Complete response	1 (4.2)	1 (5.3)	0
Partial response	4 (16.7)	4 (21.1)	0
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)
ORR, n (%) [95% CI]	5 (20.8) [7.1, 42.2]	5 (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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Best Reduction in Target Lesions

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



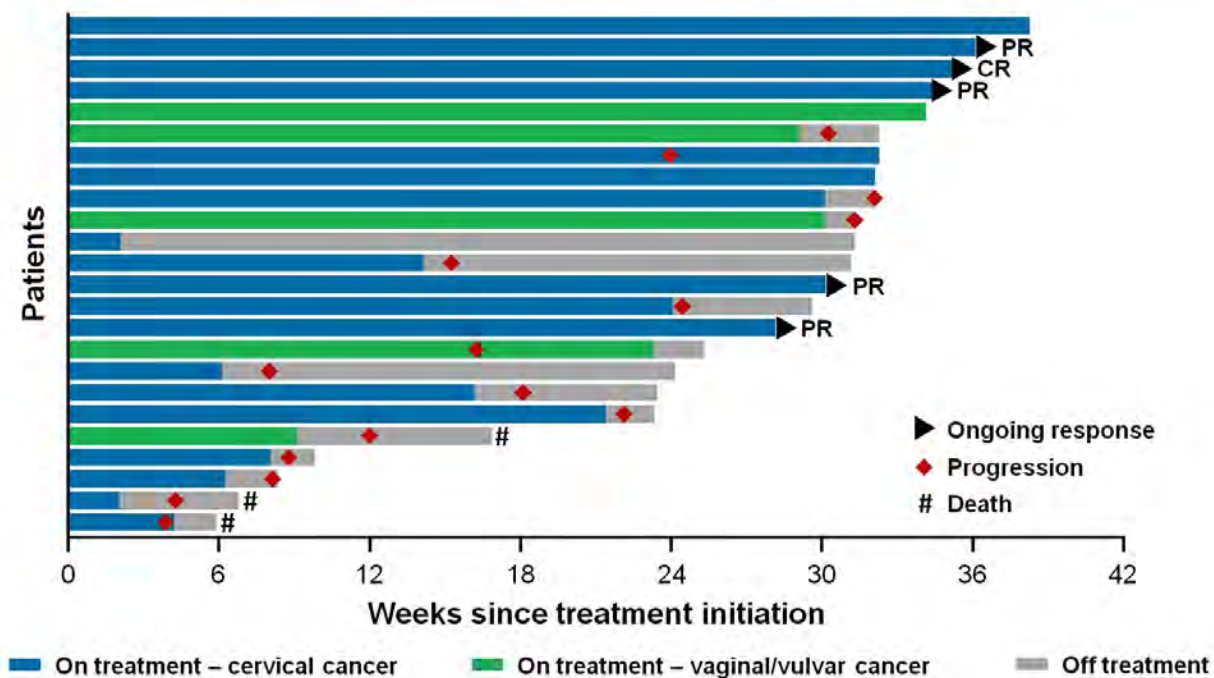
*PR not achieved as 1 patient had a new lesion and 1 patient did not have confirmed response
 1 patient is not shown due to unavailable postbaseline tumor assessment prior to subsequent anti-cancer therapy
 CR = complete response; PR = partial response

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CheckMate 358

Duration of Treatment

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



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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 (%)	2 (28.6)	3 (17.6)
[95% CI]	[3.7, 71.0]	[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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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)

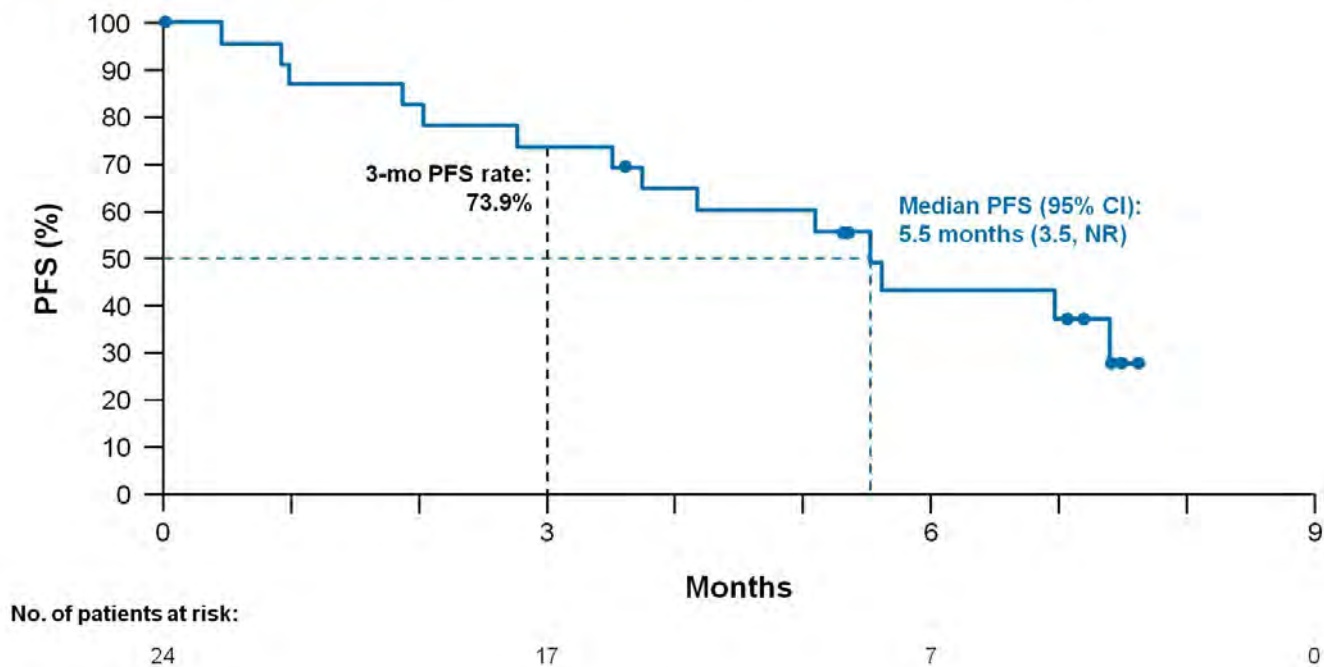
As respostas correlacionam-se tanto com a expressão de PD-L1 quanto com a infecção por HPV.

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CheckMate 358

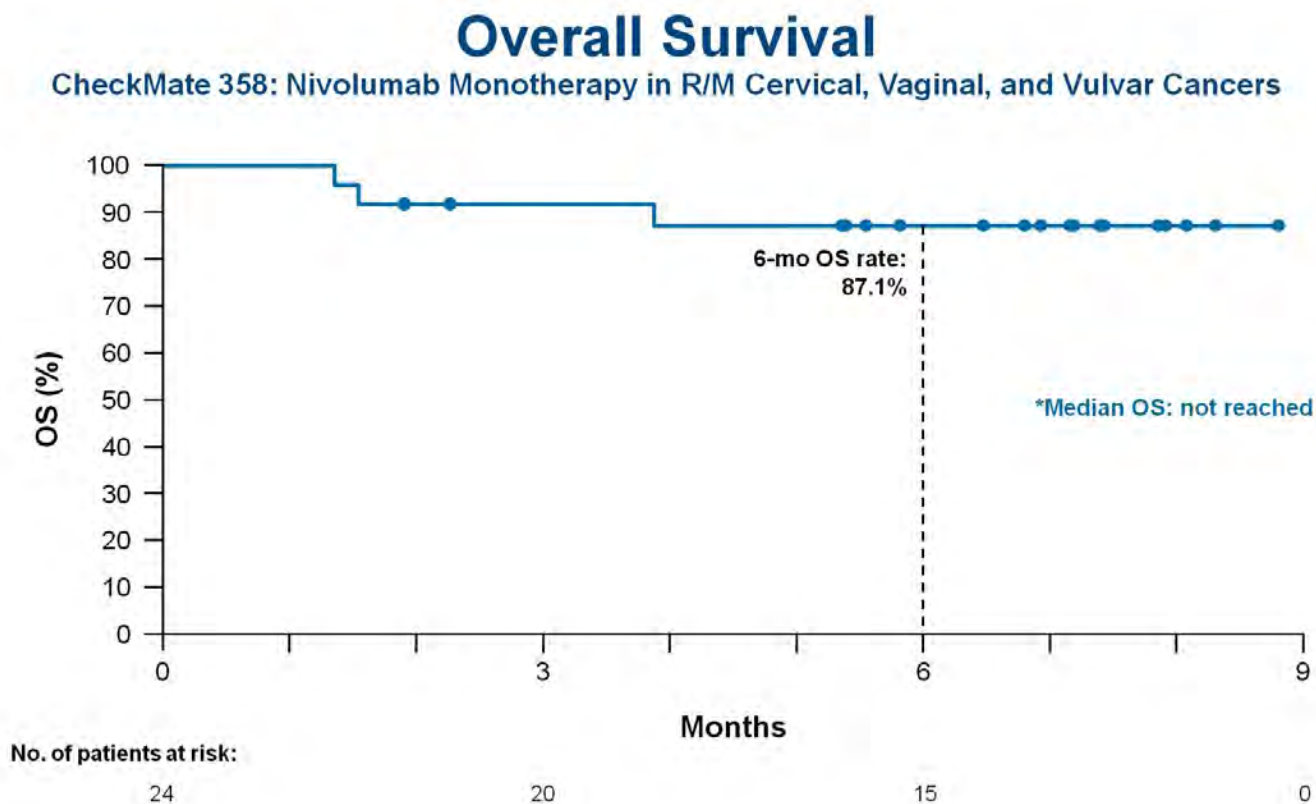
Progression-Free Survival

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



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CheckMate 358



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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

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- 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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