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APOIO

Instituto Projeto
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REALIZAÇÃO



GERENCIAMENTO
E PRODUÇÃO



O papel da carboplatina no tratamento do câncer de mama triplo negativo inicial

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Declaração Conflito de Interesses

Considerando o disposto nas resoluções do Conselho Federal de Medicina (CFM n° 1.595/00 de 18/05/2000) e da Agência Nacional de Vigilância Sanitária (ANVISA n° 96/08), DECLARO que:

1) Recebo honorária como “speaker” das seguintes empresas:

Roche ; AstraZeneca; Eli Lilly; Novartis; Pfizer; MSD; DSBR; Gilead

2) Participo como pesquisador em estudos patrocinados pelas seguintes empresas:

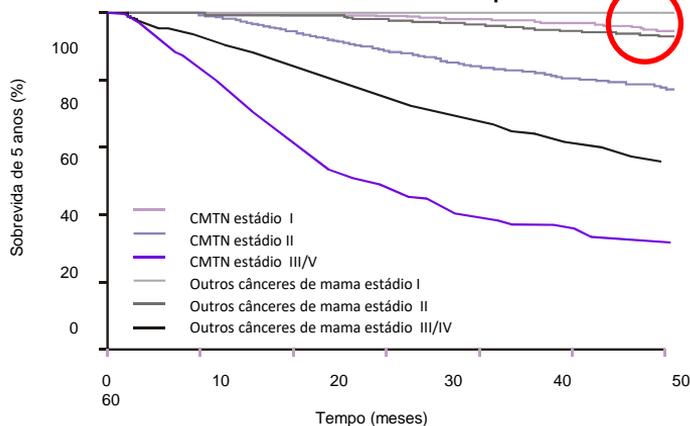
Novartis; MSD; BMS; Roche; AstraZeneca

“Outline”

- ***Prognóstico cancer de mama triplo negativo (CMTN) inicial***
- ***Tratamento sistêmico adjuvante: benefício carboplatina***
- ***Tratamento sistêmico neoadjuvante: benefício adição da carboplatina***
- ***Tratamento sistêmico neoadjuvante: opções de descalonamento***
- ***Conclusões***

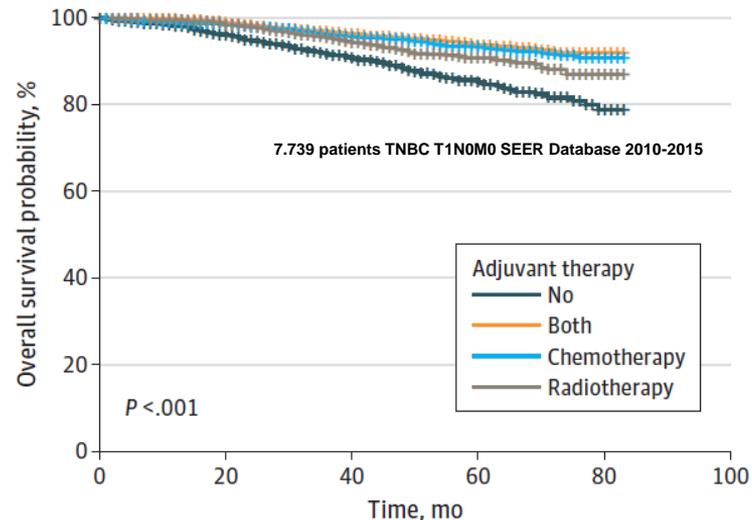
Prognóstico CMTN Inicial

Sobrevida Geral por Estádio da Doença de Mulheres com CMTN ou Outros Subtipos^{1,2}



1. Pal et al. Breast Cancer Res Treat 2011; 2. Bauer et al. Cancer 2007

Overall survival probability of patients with T1N0M0 TNBC according to adjuvant therapies



Zai Z et al. Jama Network Open. 220;3(11):e2021881

Tratamento sistêmico adjuvante Para qual paciente?

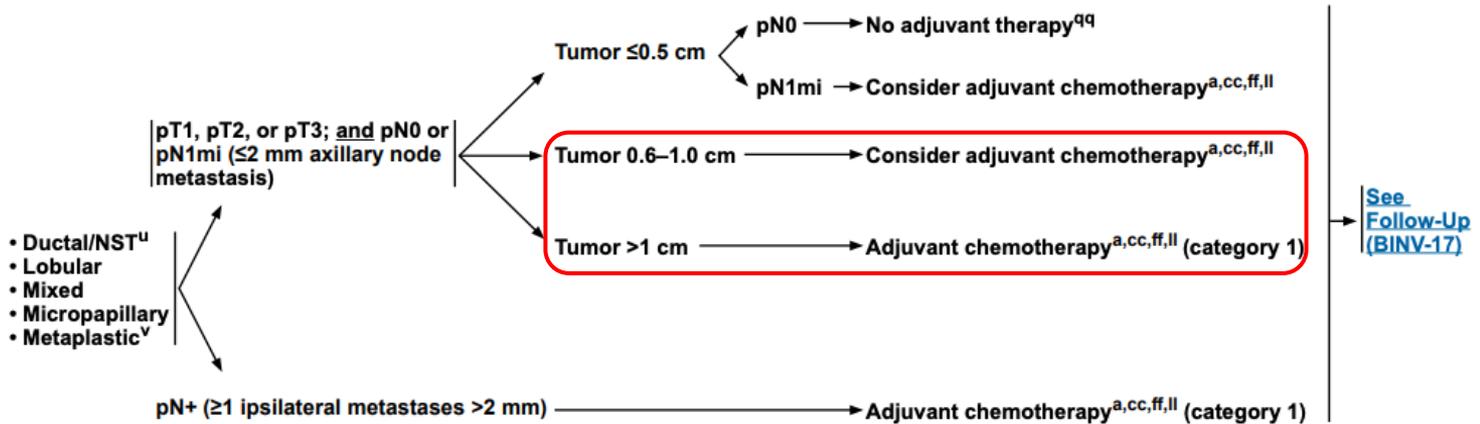


National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2023 Invasive Breast Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

SYSTEMIC ADJUVANT TREATMENT: HR-NEGATIVE - HER2-NEGATIVE DISEASE^{d,r,z}



Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

JAMA Oncology | Original Investigation

Effect of Adjuvant Paclitaxel and Carboplatin on Survival
in Women With Triple-Negative Breast Cancer
A Phase 3 Randomized Clinical Trial

- Mulheres câncer de mama triplo negativo, T >1 cm ou N+.
- Submetidas à cirurgia
- ECOG 0-2, 18-70 anos
- Julho 2011 a Abril 2016
- N=672

Randomização
(1:1)

Stratificado pelo
status nodal, idade,
pT1 vs T2-3

Paclitaxel 80mg/m² +
carbo AUC 2 D1, D8 e
D15 a cada 28 dias – 6
ciclos

FEC –T (FU 500mg/m² +
Epi 100mg/m² + Ciclo
500mg/m² – Docetaxel
100mg/m²) 6 ciclos

- Desfecho Primário
- DFS
- Desfechos Secundários
- Chaves
 - DDFS
 - RFS
 - OS
 - Toxicidade

Table 1. Patient Characteristics by Treatment Group

Characteristic	No. (%)		
	Total (N = 647)	CEF-T (n = 322)	PCb (n = 325)
Pathologic tumor size			
pT1	351 (54.2)	173 (53.7)	178 (54.8)
pT2-pT3	296 (45.8)	149 (46.3)	147 (45.2)
Node status			
Negative	481 (74.3)	244 (75.8)	237 (72.9)
Positive	166 (25.7)	78 (24.2)	88 (27.1)
Histological grade			
I-II	177 (27.4)	88 (27.3)	89 (27.4)
III	470 (72.6)	234 (72.7)	236 (72.6)
BRCA1/2 genes			
Deleterious variant ^a	66 (10.2)	32 (9.9)	34 (10.5)
No deleterious variant	472 (73.0)	237 (73.6)	235 (72.3)
Unknown	109 (16.8)	53 (16.5)	56 (17.2)

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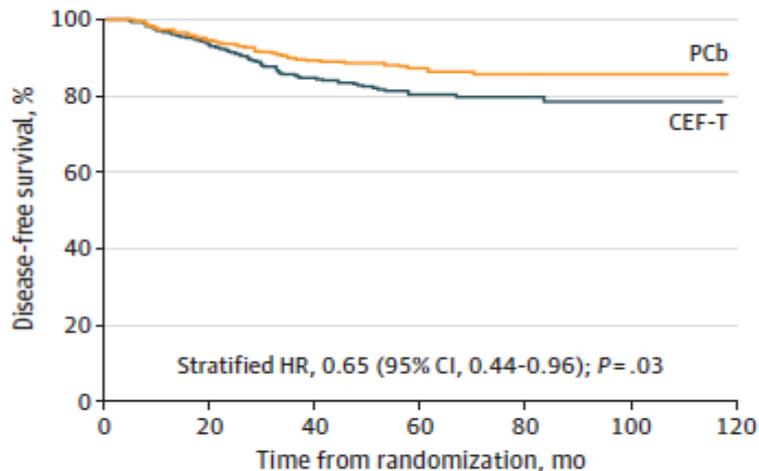


GERENCIAMENTO E PRODUÇÃO



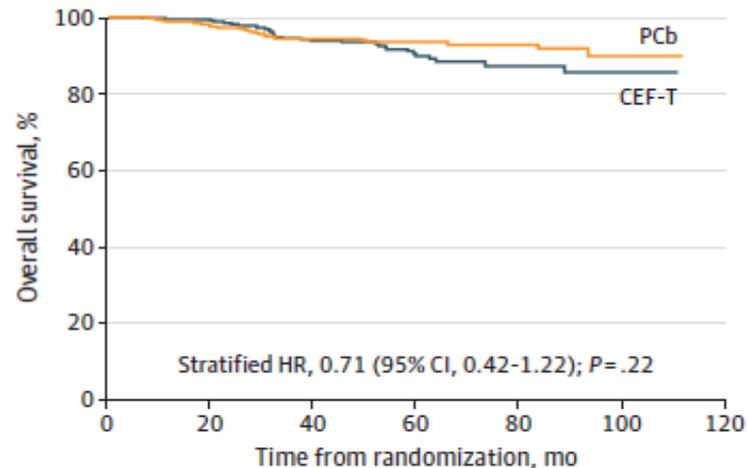
Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

A Disease-free survival



No. at risk	0	20	40	60	80	100	120
CEF-T group	322	295	266	146	69	12	0
PCb group	325	302	278	166	89	28	0

B Overall survival



No. at risk	0	20	40	60	80	100	120
CEF-T group	322	306	276	150	72	13	0
PCb group	325	307	278	168	71	28	0

Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

Trial	N	Drogas	População	pCR	EFS
Geparsixto	165	PM/Bev PMCb/Bev	TNBC (subgrupo)	36.9% 53.2% ↑ 16.3%	76.1% 85.8% HR: 0.55
CALGB 40603	455	T-AC(bev) T/carbo-AC(bev)	TNBC (subgrupo)	41% 54% ↑ 13.0%	HR 0.99
BrighTNess	634	T-AC T/Carbo-AC T/Carbo/Veliparib-AC	TNBC	31% 58% 53% ↑ 27.0%	68.5% 79.3% 78.2% HR: 0.57 HR: 0.57

Vom Minckwitz G et al. JAMA Oncol 2017

Sikov WM et al. Cancer Res. 2016

Loibl S et al. Lancet Oncol 2018

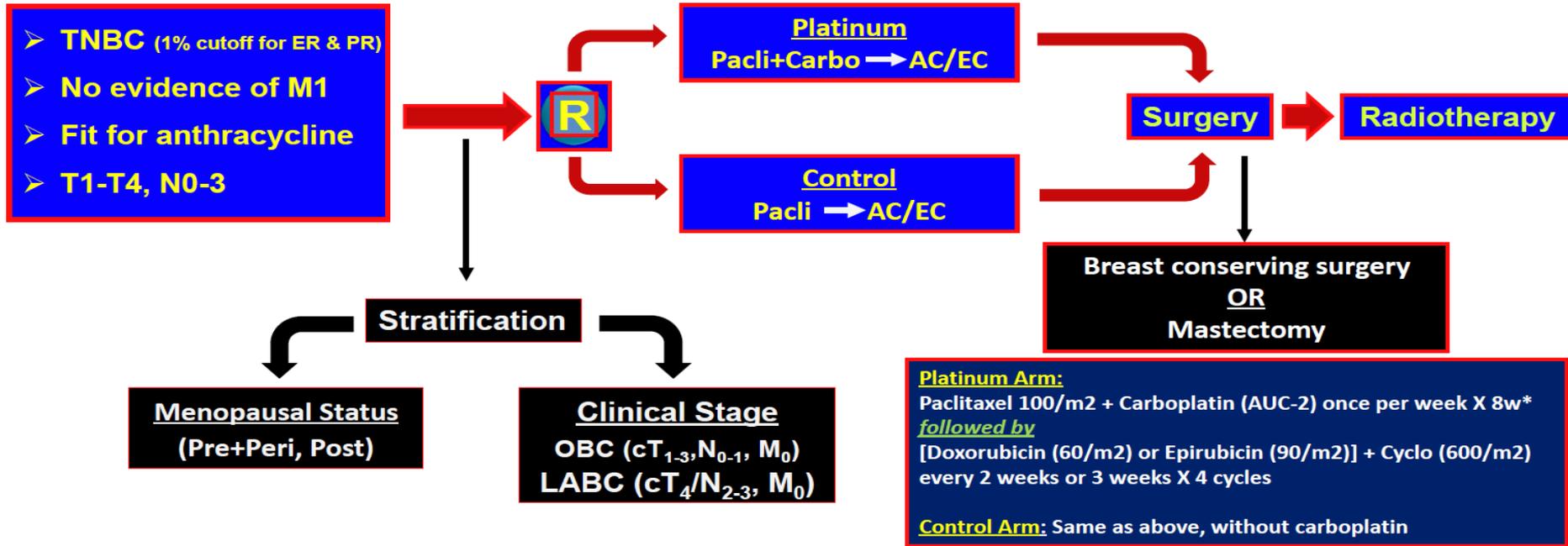
Loibl S et al. ESMO 2021

Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

Brightness Trial

	Paclitaxel + carboplatin + veliparib (n=313)			Paclitaxel + carboplatin + veliparib placebo (n=158)			Paclitaxel + carboplatin placebo + veliparib placebo (n=157)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Blood and lymphatic system disorders									
Neutropenia	40 (13%)	138 (44%)	41 (13%)	13 (8%)	66 (42%)	18 (11%)	11 (7%)	3 (2%)	1 (1%)
Anaemia	114 (36%)	77 (25%)	0	65 (41%)	27 (17%)	0	17 (11%)	0	0
Leukopenia	27 (9%)	12 (4%)	1 (<1%)	17 (11%)	7 (4%)	1 (1%)	5 (3%)	1 (1%)	0
Thrombocytopenia	117 (37%)	27 (9%)	6 (2%)	49 (31%)	8 (5%)	2 (1%)	0	0	0
Febrile neutropenia	0	5 (2%)	0	0	1 (1%)	0	0	0	0
Lymphopenia	5 (2%)	0	0	0	0	0	2 (1%)	2 (1%)	0

Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina



Gupta S et al. SABCs 2022

Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

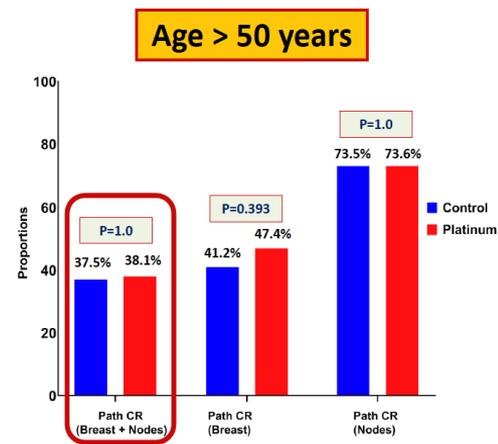
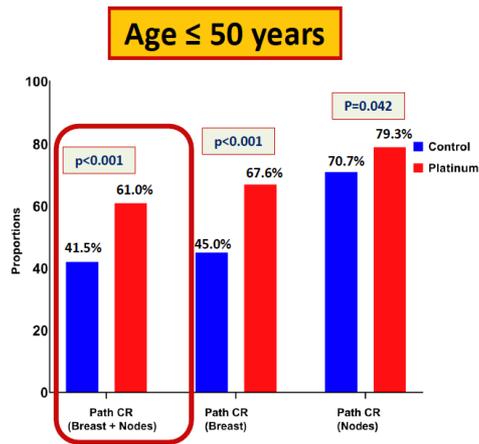
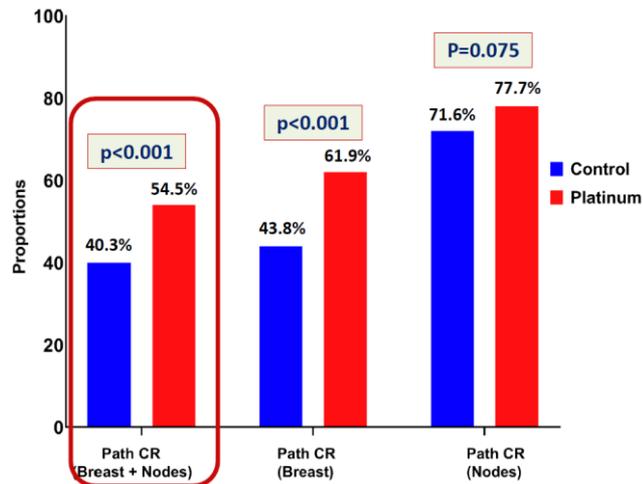
Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
<u>Clinical Stage (pre-NACT)</u>			
Operable (cT1-3, N0-1)	142 (39.9%)	143 (39.6%)	285 (39.7%)
Locally Advanced (cT4 / N2-3)	214 (60.1%)	218 (60.4%)	432 (60.3%)
<u>Clinical Node Status (pre-NACT)</u>			
Negative	39 (11.0%)	41 (11.4%)	80 (11.2%)
Positive	317 (89.0%)	320 (88.6%)	637 (88.8%)
<u>Clinical T-size (pre-NACT) (cm)</u>			
Median (Range)	6.0 (1.2-20.0)	6.0 (1.5-20.0)	6.0 (1.2-20.0)
≤ 5 cm	79 (22.2%)	81 (22.4%)	160 (22.3%)
> 5 cm	277 (77.8%)	280 (77.6%)	557 (77.7%)

Gupta S et al. SABCS 2022

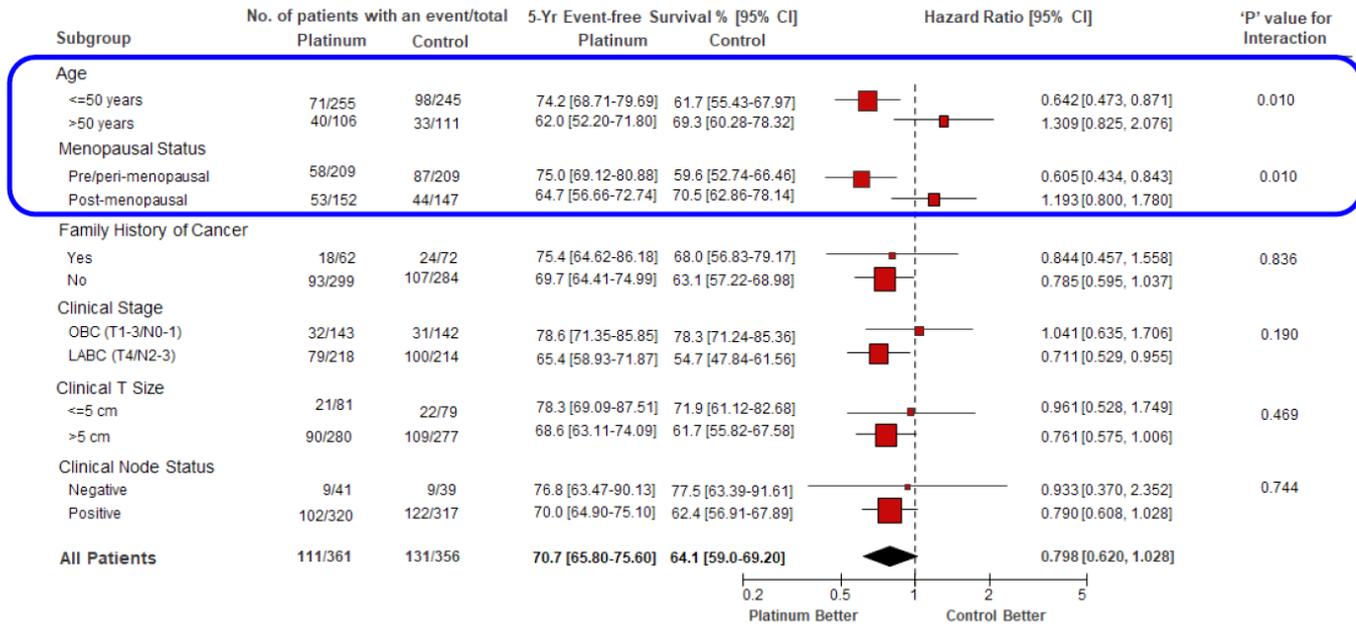
Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

ITT: Pathological Response to NACT by Rx-Arm Pathological Response to NACT by Age & Rx-Arm

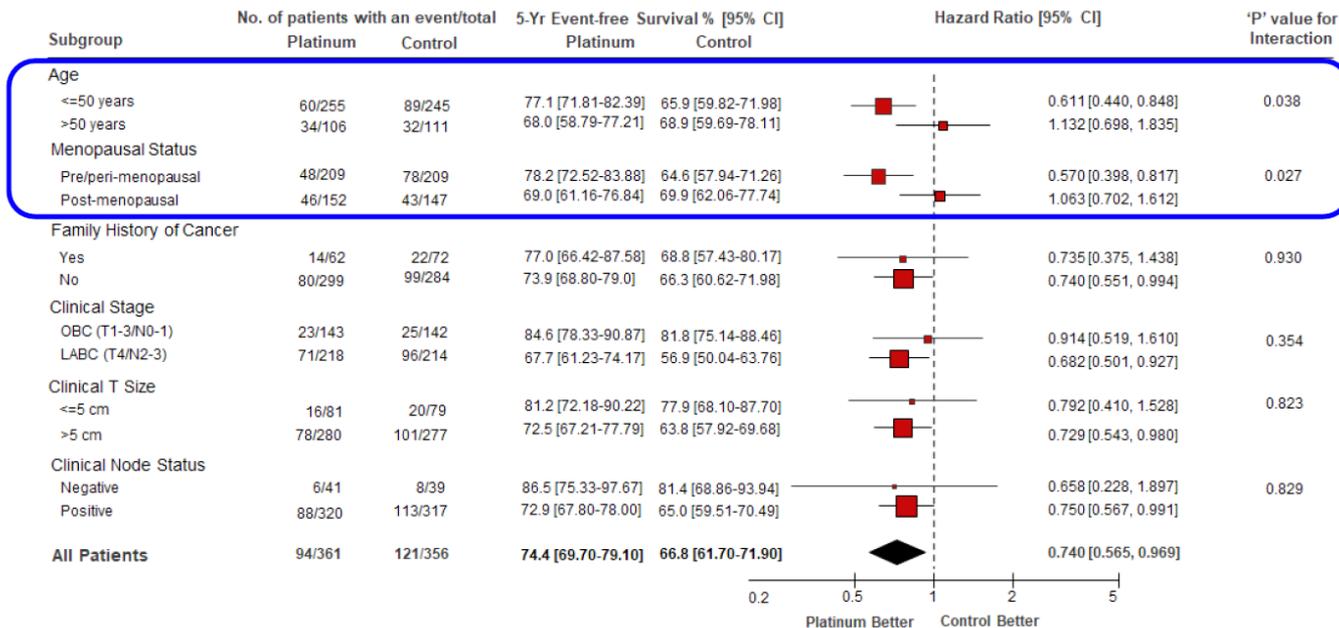


Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

Event-free Survival: Subgroup Analysis



Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina Overall Survival: Subgroup Analysis



Tratamento sistêmico adjuvante: Benefício Adição da Carboplatina

Trial	N	Drogas	População	pCR	EFS
Geparsixto	165	PM/Bev PMCb/Bev	TNBC (subgrupo)	36.9% 53.2% ↑ 16.3%	76.1% 85.8% HR: 0.55
CALGB 40603	455	T-AC(bev) T/carbo-AC(bev)	TNBC (subgrupo)	41% 54% ↑ 13.0%	HR 0.99
BrightNness	634	T-AC T/Carbo-AC T/Carbo/Veliparib-AC	TNBC	31% 58% 53% ↑ 27.0%	68.5% 79.3% 78.2% HR: 0.57
TMC 2022	720 (70% <50a)	T-AC/EC T/carbo-AC/EC	TNBC	40.3% 54.5% ↑ 14.2%	62.0% 74.2% (<50a) HR: 0.64

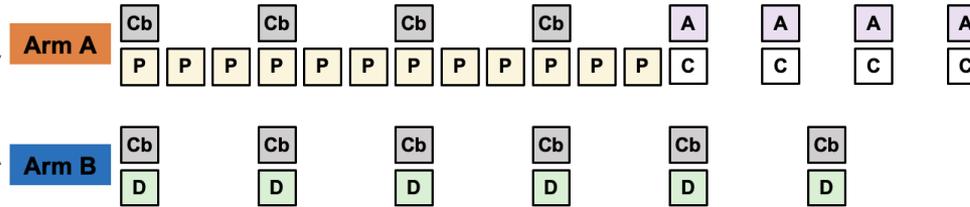
Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoSTOP Trial

**Treatment
18-20 weeks**

Stage I-III
TNBC^a
T >1 cm or N+
N=100

R^b
1
1



Surgery

Cb Carboplatin P Paclitaxel A Adriamycin C Cytosin D Docetaxel

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoSTOP Trial

Characteristic		All Patients (N=100)	Arm A (N=48)	Arm B (N=52)	P
T stage	T 1	19 (19%)	11 (23%)	8 (15%)	0.46
	T 2	70 (70%)	31 (65%)	39 (75%)	
	T 3-4	11 (11%)	6 (12%)	5 (10%)	
Lymph node status	Negative	70 (70%)	34 (71%)	36 (69%)	1.00
	Positive	30 (30%)	14 (29%)	16 (31%)	
ER/PgR IHC	0%	84 (84%)	39 (81%)	45 (87%)	0.59
	1-10%	16 (16%)	9 (19%)	7 (13%)	

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoSTOP Trial

Adverse Events	Arm A (CbP→AC) N (%)	Arm B (CbD) N (%)	P
Anemia^a	22 (46%)	2 (4%)	0.0001
Neutropenia	29 (60%)	4 (8%)	0.0001
Thrombocytopenia	8 (17%)	2 (4%)	0.05
Febrile neutropenia^b	9 (19%)	0	<0.001
Hypokalemia	2 (4%)	1 (2%)	0.61
Hyponatremia	2 (4%)	1 (2%)	1
Nausea	1 (2%)	0	0.48
Constipation	1 (2%)	0	0.48
Diarrhea	1 (2%)	4 (8%)	0.36
Fatigue	1 (2%)	0	0.48
Pain	1 (2%)	1 (2%)	1
Peripheral sensory neuropathy	2 (4%)	0	0.23
Rash	0	2 (4%)	0.50
Infection	3 (6%)	0	0.23

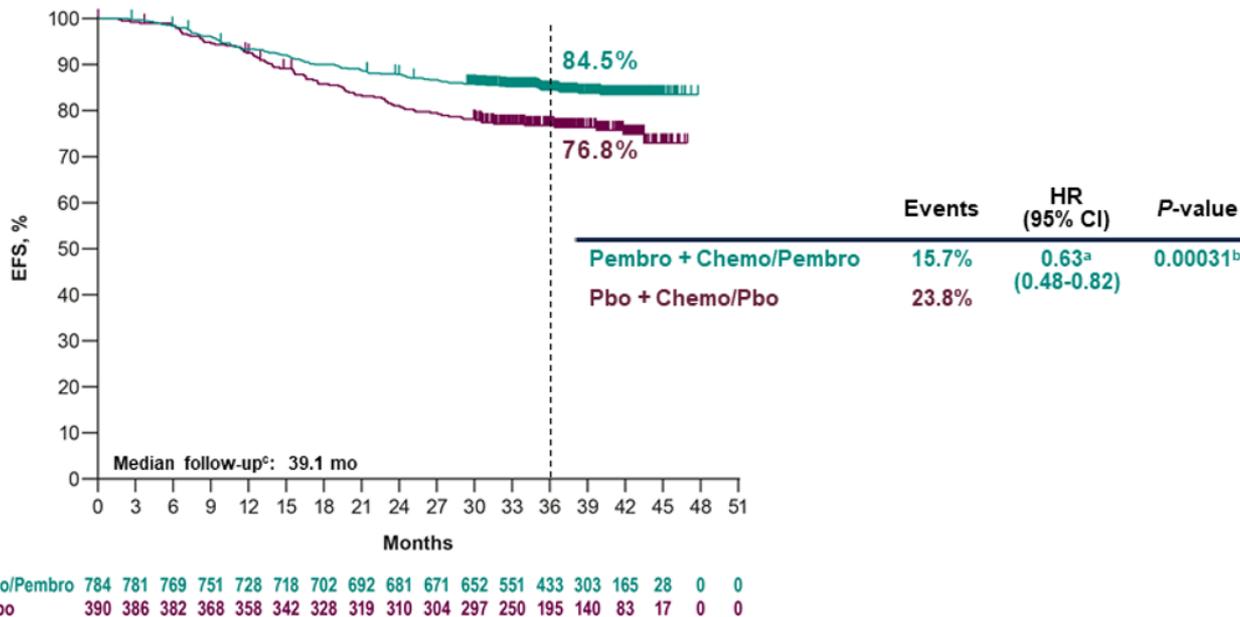
Sharma P et al. Clin Cancer Res. 2021 Feb 15;27(4):975-982

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

	I-SPY 2 Pembrolizumab e	KEYNOTE-522 Pembrolizumabe	NEOTRIP Atezolizumabe	Impassion 031 Atezolizumabe	GEPARNUEVO Durvalumabe
N	181	1174	280	333	174
Desenho	Fase II	Fase III	Fase III	Fase III	Fase II
Alvo	PD-1	PD-1	PD-L1	PD-L1	PD-L1
TNM	II/III	II/III	I-III	II/III	I-III
Antraciclina	SIM	SIM	NÃO	SIM	SIM
Carboplatina	NÃO	SIM	SIM	NÃO	NÃO
Taxa pCR	60% vs 22%	65% vs 51% (p=0.00055)	48.6% vs 44.4% (p=0.48)	57.6 vs 41.1% (p=0.0044)	53% vs 44% (p=0.287)

1) Nanda R et al. JAMA Oncol. 2020 May 1;6(5):676-684. 2) Schmid P et al. N Engl J Med 2020 3) Gianni L et al. Ann Oncol. 2022 Feb 17:S0923-7534. 4) Mittendorf EA et al. Lancet. 2020 Oct 10;396(10257):1090-1100. 5) Loibl S et al. Ann Oncol. 2019 Aug 1;30(8):1279-1288.

Tratamento sistêmico neoadjuvante: Opções de Descalonamento



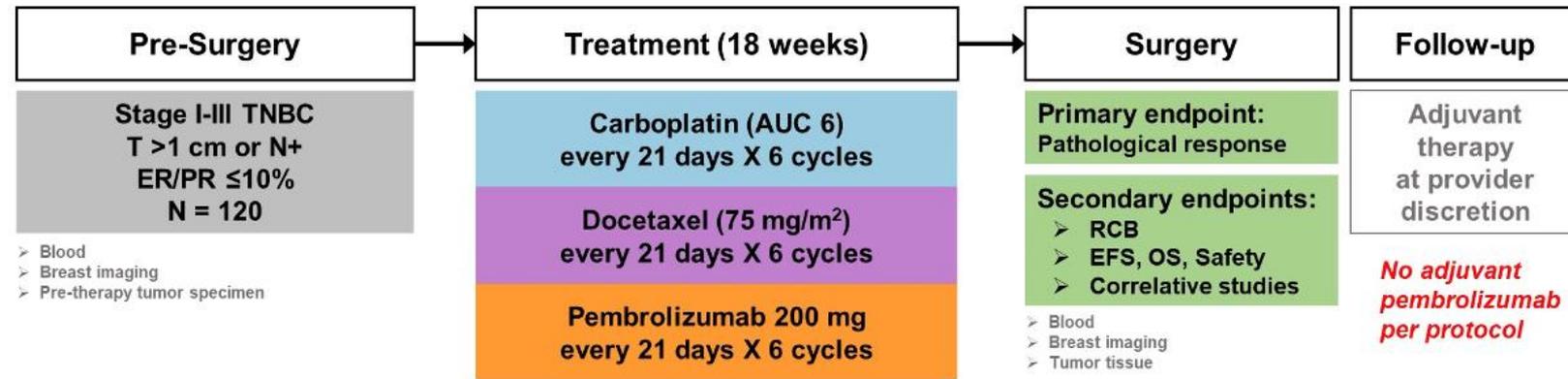
Schmid P et al. ESMO 2021

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

2022 ASCO
ANNUAL MEETING

Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)

Priyanka Sharma, Shane R. Steeklein, Rachel Yoder, Joshua M. Staley, Kelsey Schwensen, Anne O'Dea, Lauren Nye, Mariana Eisa, Deepthi Satelli, Gregory Crane, Rashna Madan, Maura F. O'Neil, Jamie Wagner, Kelsey E. Larson, Christa Balanoff, Millind A. Phadnis, Andrew K. Godwin, Roberto Salgado, Qamar J. Khan, Joyce O'Shaughnessy



Sharma P et al. ASCO 2022

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoPACT Trial

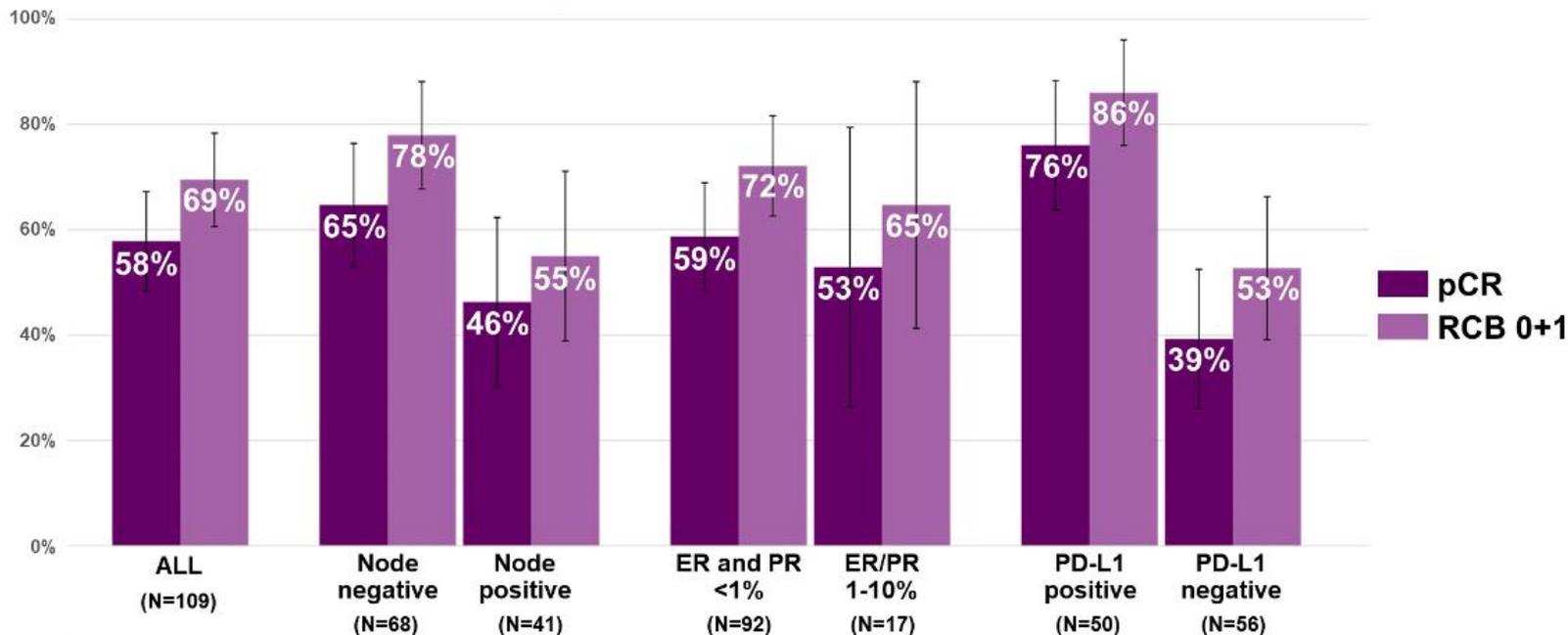
Characteristic – N (%)		N=115
Age at diagnosis, yrs – median (range)		50 (27-70)
Race	White	84 (73%)
	Black	20 (17%)
	Other	10 (9%)
Ethnicity ^a	Non-Hispanic	111 (97%)
	Hispanic	3 (3%)
Menopausal status	Pre	58 (50%)
	Post	57 (50%)
Germline <i>BRCA1/2</i> mutation	Yes	9 (8%)
	No	95 (83%)
	Unknown	11 (10%)
T stage	1	21 (18%)
	2	73 (63%)
	3	21 (18%)
Nodal status	Negative	70 (61%)
	Positive ^b	45 (39%)
TNM stage	I	14 (12%)
	II	86 (75%)
	III	15 (13%)
ER/PR (IHC)	ER and PR <1%	97 (84%)
	ER and/or PR 1-10%	18 (16%)

Characteristic – N (%), cont.		N=115
sTILs, % – median (range) ^c		20 (1-95)
sTILs ^c	<30%	56 (52%)
	≥30%	51 (48%)
PD-L1 (CPS ≥10) ^d	Positive	52 (46%)
	Negative	60 (54%)
Surgery type ^e	Lumpectomy	54 (48%)
	Mastectomy	58 (52%)
Adjuvant radiation therapy ^f		80 (74%)
Adjuvant immunotherapy ^g		5 (5%)
Adjuvant chemotherapy ^g		38 (35%)
Anthracycline + cyclophosphamide (AC)		18 (17%)
Capecitabine		11 (10%)
AC and capecitabine		7 (6%)
Other		2 (2%)

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoPACT Trial

RESULTS: Pathologic response

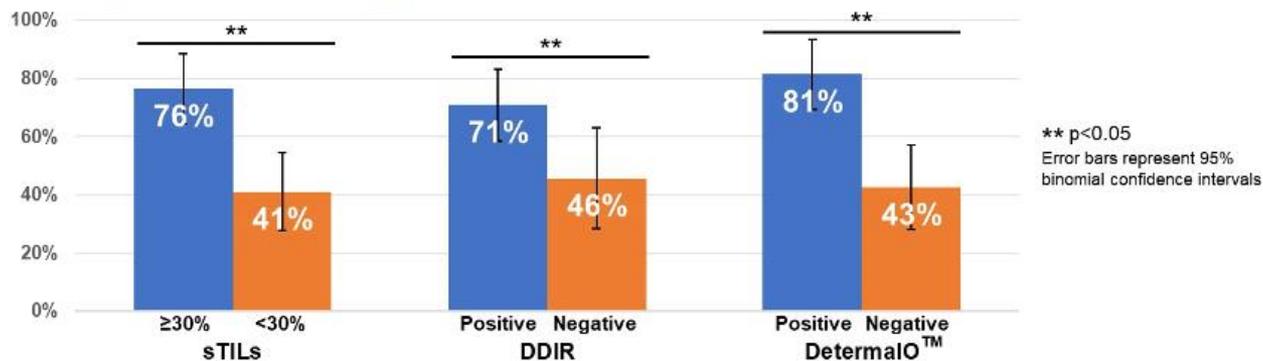


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Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoPACT Trial

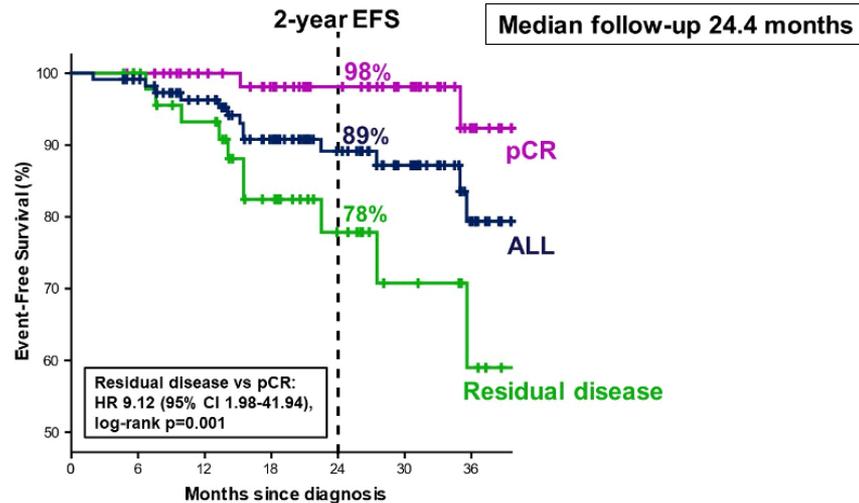
Pathologic response by immune markers



Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoPACT Trial

Event-free survival



	Number at risk						
	0	6	12	18	24	30	36
All	113	108	95	75	54	37	18
pCR	63	62	55	48	38	28	13
Residual disease	49	46	40	27	16	9	5

Survival analysis includes all patients in the ITT population except for N=2 who are awaiting surgery

Sharma P et al. ASCO 2022

Tratamento sistêmico neoadjuvante: Opções de Descalonamento

NeoPACT Trial Eventos Adversos

Treatment-related adverse event ^a	All grades (N=115)	Grade 1-2	Grade 3-4
Any adverse event	115 (100.0%)	84 (73.0%)	31 (26.9%)
Fatigue	87 (75.7%)	86 (74.8%)	1 (0.9%)
Diarrhea ^b	72 (62.6%)	67 (58.3%)	5 (4.3%)
Nausea	68 (59.1%)	66 (57.1%)	2 (1.7%)
Peripheral sensory neuropathy ^c	46 (40.0%)	43 (37.4%)	3 (2.6%)
Constipation	43 (37.4%)	43 (37.4%)	0 (0%)
Dysgeusia	40 (34.8%)	40 (34.8%)	0 (0%)
Alopecia	39 (33.9%)	39 (33.9%)	0 (0%)
Mucositis oral	39 (33.9%)	39 (33.9%)	0 (0%)
Arthralgia	32 (27.8%)	32 (27.8%)	0 (0%)
Watering eyes	27 (23.5%)	27 (23.5%)	0 (0%)
Rash	27 (23.5%)	26 (22.6%)	1 (0.9%)
Edema limbs	26 (22.6%)	26 (22.6%)	0 (0%)
Anorexia	25 (21.7%)	25 (21.7%)	0 (0%)
Myalgia	24 (20.9%)	24 (20.9%)	0 (0%)
Anemia	20 (17.4%)	16 (12.2%)	4 (3.5%)
Bone pain	20 (17.4%)	20 (17.4%)	0 (0%)
Nail discoloration	19 (16.5%)	19 (16.5%)	0 (0%)
Insomnia	18 (15.7%)	18 (15.7%)	0 (0%)
Headache	16 (13.9%)	16 (13.9%)	0 (0%)
Hot flashes	15 (13.0%)	14 (12.2%)	1 (0.9%)
Abdominal pain	14 (12.2%)	14 (12.2%)	0 (0%)
Dyspnea	13 (11.3%)	13 (11.3%)	0 (0%)
Fever	13 (11.3%)	12 (10.4%)	1 (0.9%)
Hypomagnesemia	13 (11.3%)	12 (10.4%)	1 (0.9%)
Dehydration	12 (10.4%)	10 (8.7%)	2 (1.7%)
Vomiting	11 (9.6%)	11 (9.6%)	0 (0%)

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Conclusões

Carboplatina no câncer de mama triplo negativo inicial:

Adjuvância: cT1bcN0

- **Benefício EFS – estudo único (Carbo + Paclitaxel)**
- **Pacientes de maior risco – antraciclinas e taxanos**

Neoadjuvância: cT2N0 ou N+

- ***Conversão cirúrgica e redução da morbidade axillar***
- ***Benefício significativo em pCR***
- ***Benefício em EFS, opção para esquemas sem antraciclina***
- ***Possibilidade de descalonamento da QT com carbo e imunoterapia***

OBRIGADO!

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