



Algoritmo do tratamento do câncer de mama inicial HER2-positivo em 2023

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POTENCIAIS CONFLITOS DE INTERESSE

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro:

- Advisory Boards:
 - Novartis; Roche; Libbs; Teva; Amgen; Genomic Health; AstraZeneca
- Palestras:
 - Roche; Genomic Health/Fleury; Libbs; Novartis; Pfizer; AstraZeneca; Daiichi-Sankyo
- Estudos Clínicos (como PI):
 - Novartis; Libbs; Roche

Não possuo ações de empresas da indústria farmacêutica

CÂNCER DE MAMA HER2-POSITIVO NÃO METASTÁTICO

Como conduzir em 2023?

AXILA CLINICAMENTE NEGATIVA e T \leq 2cm?

SIM

CIRURGIA UPFRONT

pN0?

SIM

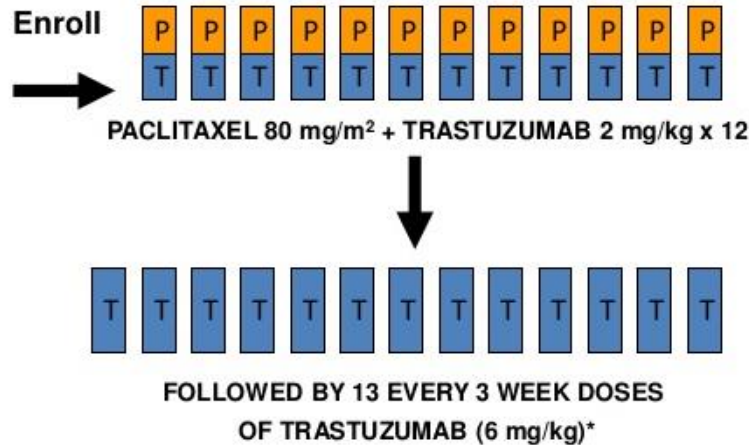
TH

Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial



Sara M Tolaney, Paolo Tarantino, Noah Graham, Nabihah Tayob, Laia Parè, Guillermo Villacampa, Chau T Dang, Denise A Yardley, Beverly Moy, P Kelly Marcom, Kathy S Albain, Hope S Rugo, Matthew J Ellis, Iuliana Shapira, Antonio C Wolff, Lisa A Carey, Romualdo Barroso-Sousa, Patricia Villagrasa, Michelle DeMeo, Molly DiLullo, Jorge Gomez Tejada Zanudo, Jakob Weiss, Nikhil Wagle, Ann H Partridge, Adrienne G Waks, Clifford A Hudis, Ian E Krop, Harold J Burstein, Aleix Prat, Eric P Winer

Câncer de mama
≤ 3cm, axila
negativa, HER2+
RE + ou RE -
N=406



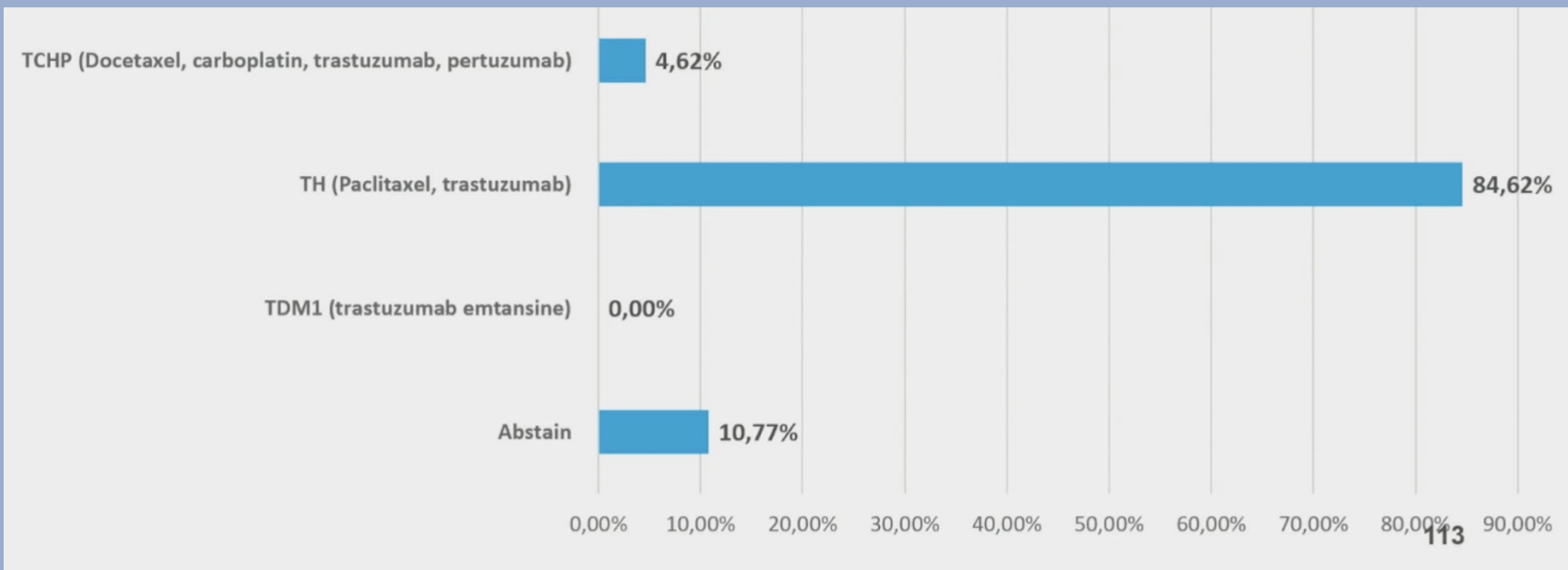
SABCS 2022

Seguimento mediano de 10,8 meses
6 recorrências à distância (1,5%)
BCSS 98,8%

Tolaney et al. Lancet Oncol 2023; 24: 273–85

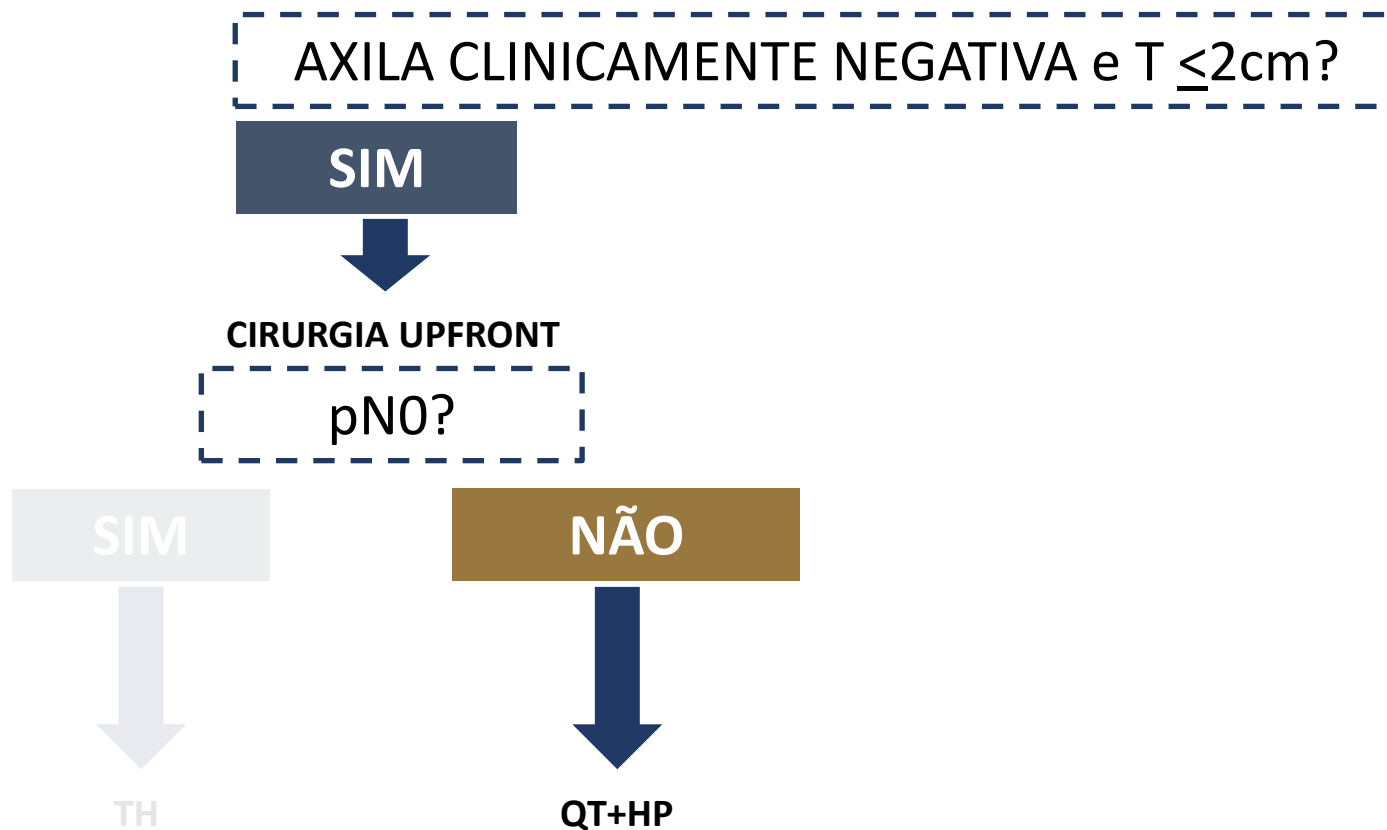
ALERTA St. Gallen 2023:

Tratamento adjuvante preferencial para paciente com câncer de mama estágio I HER2-positivo?



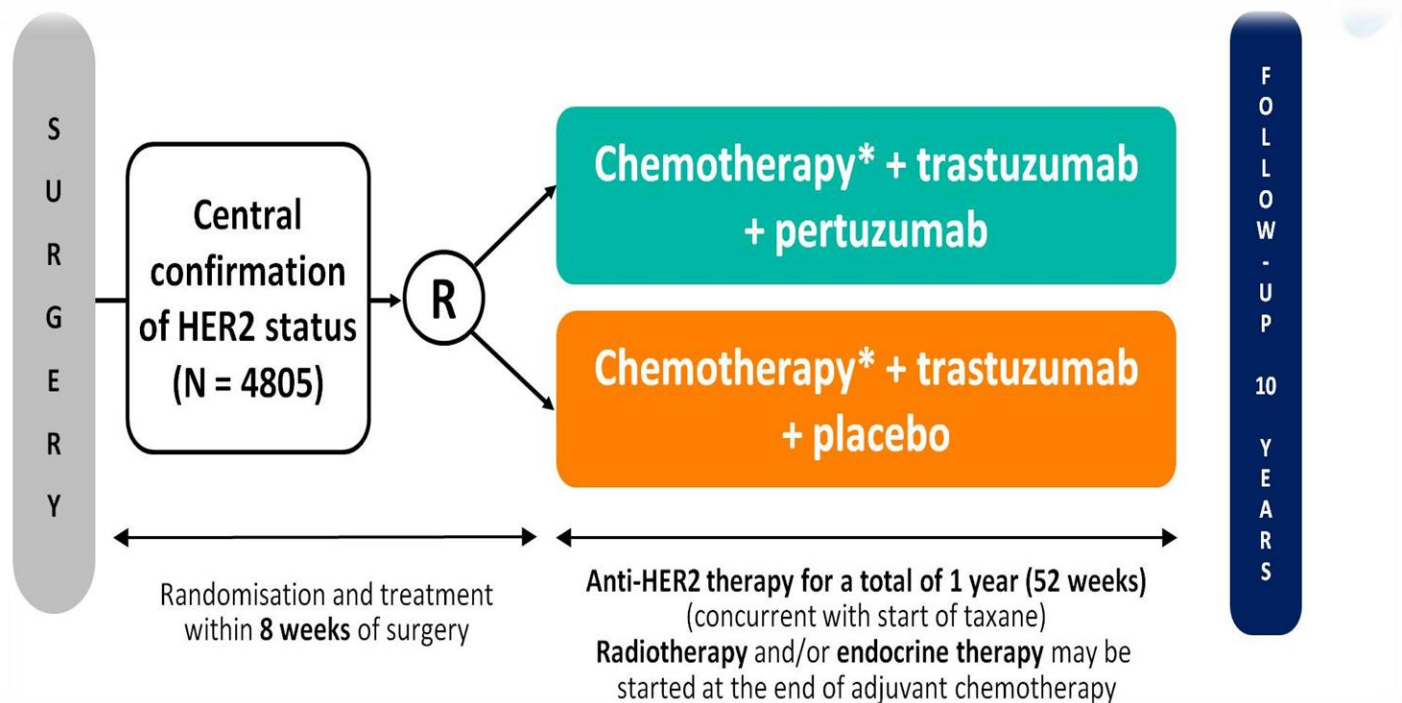
CÂNCER DE MAMA HER2-POSITIVO NÃO METASTÁTICO

Como conduzir em 2023?



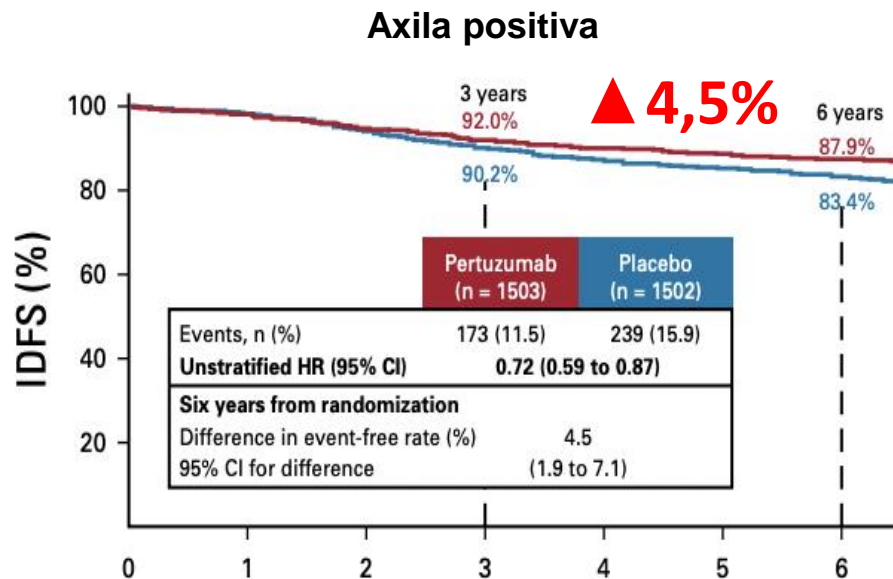
Fase 3 APHINITY

Duplo bloqueio HP na adjuvância



Fase 3 APHINITY

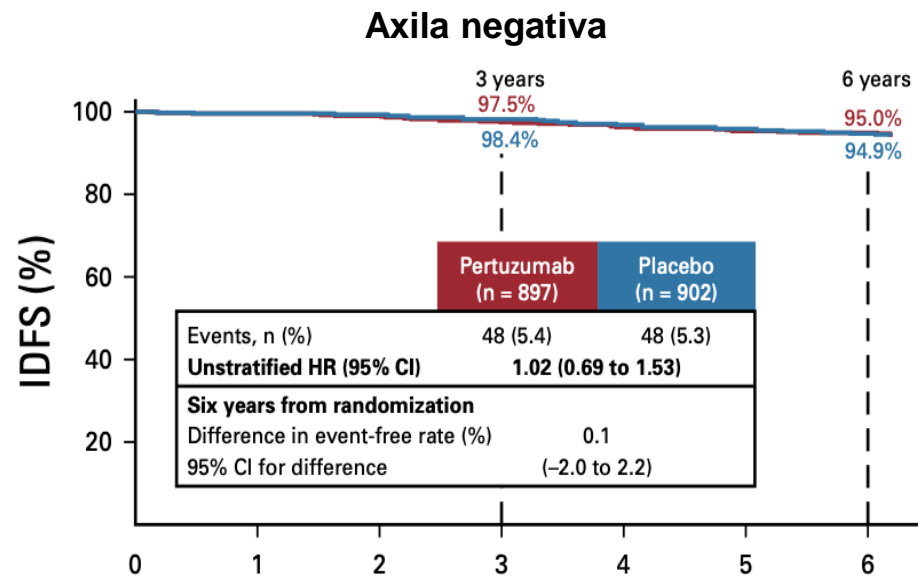
Duplo bloqueio HP na adjuvância



Years From Random Assignment

No. patients at risk

1,503	1,420	1,357	1,301	1,257	1,205	814
1,502	1,439	1,359	1,288	1,223	1,176	741



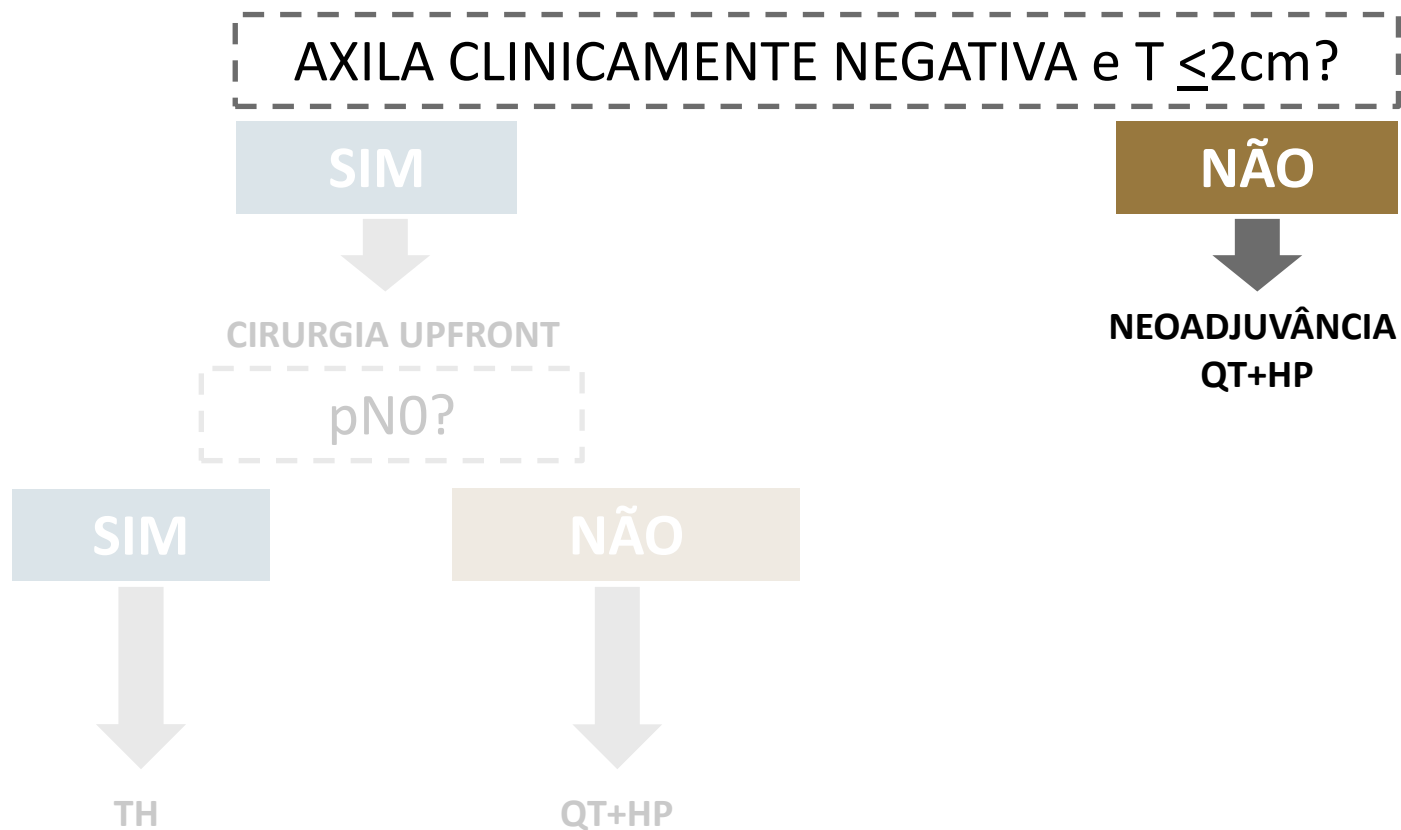
Years From Random Assignment

No. patients at risk

897	857	841	821	798	773	668
902	873	856	846	816	791	680

CÂNCER DE MAMA HER2-POSITIVO NÃO METASTÁTICO

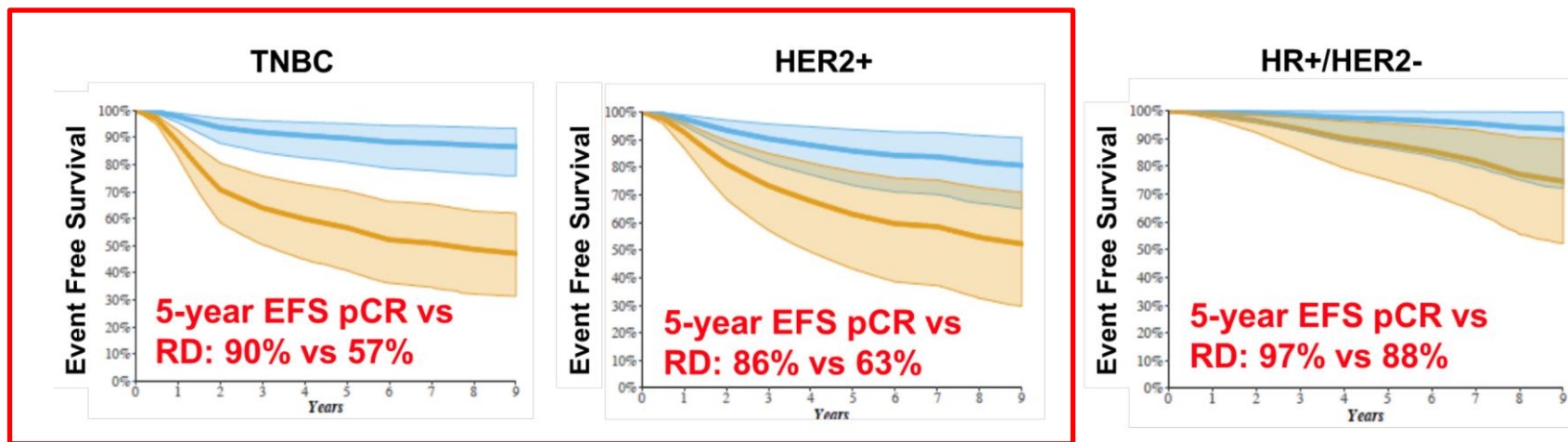
Como conduzir em 2023?



VANTAGENS DA NEOADJUVÂNCIA

- Conversão de doença inoperável em operável
- Conversão de mastectomias em cirurgias conservadoras
- Tempo para resultado de painel para câncer hereditário
- Downstaging axilar /redução das linfadenectomias
- Teste in vivo de agentes anti-neoplásicos e informação prognóstica

pCR COMO MARCADOR PARA DESFECHOS DE SOBREVIDA



Blue: pCR group

Orange: Residual disease (RD) group

*** metanálise de 52 estudos com dados individuais de 28.000 pacientes tratadas com neoadjuvância

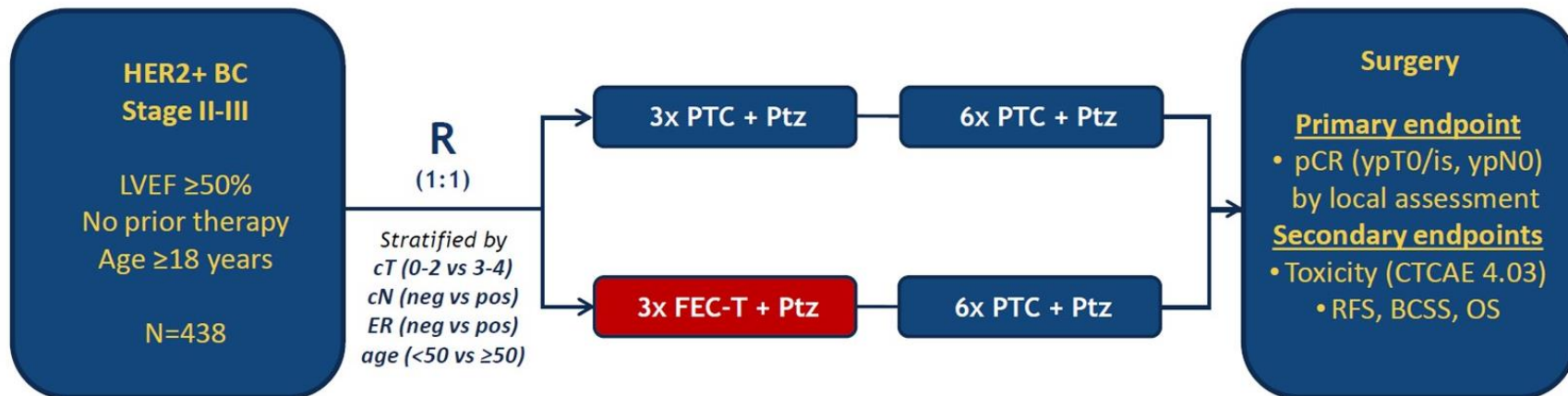
Estudos com HP neoadjuvante

ESTUDO	REGIME	DURAÇÃO	pCR	pCR (RE/RP neg)
NEOSPHERE (Fase 2 /N=417) ¹	DH	12 sem	29.0%	36.8%
	DP	12 sem	24.0%	30.0%
	DHP	12 sem	45.8%	63.2%
	HP	12 sem	16.8%	29.1%
TRYPHAENA (Fase 2 /N=225) ²	FECHP → DHP	18 sem	61.6%	79.4%
	FEC → DHP	18 sem	57.3%	65.0%
	DCbHP	18 sem	66.2%	83.3%
BERENICE (Fase 2 /N=400) ³	ddAC → THP	20 sem	61.8%	81.5%
	FEC → DHP	24 sem	60.7%	68.0%
TRAIN-2 (Fase 3 /N=438) ⁴	TCbHP	27 sem	68.0%	84.0%
	FECHP → TCbHP	27 sem	67.0%	89.0%

Fazer ou não antraciclina na doença HER2-positiva?

Fase 3 TRAIN-2

Omissão da antraciclina na doença HER2+?



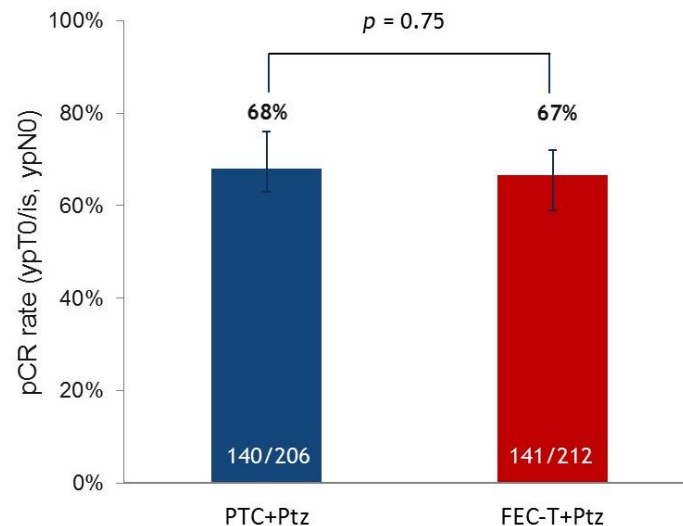
- **PTC+Ptz** cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P: P = paclitaxel 80mg/m²; T = trastuzumab 6mg/kg (loading dose 8mg/kg); C = carboplatin AUC = 6mg·min/ml; Ptz = pertuzumab, 420mg (loading dose 840mg)
- **FEC-T+Ptz** cycle of 3 weeks: F = 5-fluorouracil 500mg/m²; E = epirubicin 90mg/m²; C = cyclophosphamide 500mg/m²; T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)
- Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumors

Fase 3 TRAIN-2

Omissão da antraciclina na doença HER2+?

TRAIN-2: primary endpoint pCR

- High pathological complete response rates with and without anthracyclines
- Main outcome was consistent across levels of prespecified subgroups
 - cT (0-2 vs 3-4)
 - cN (negative vs positive)
 - HR (negative vs positive)
 - age (<50 vs ≥50)

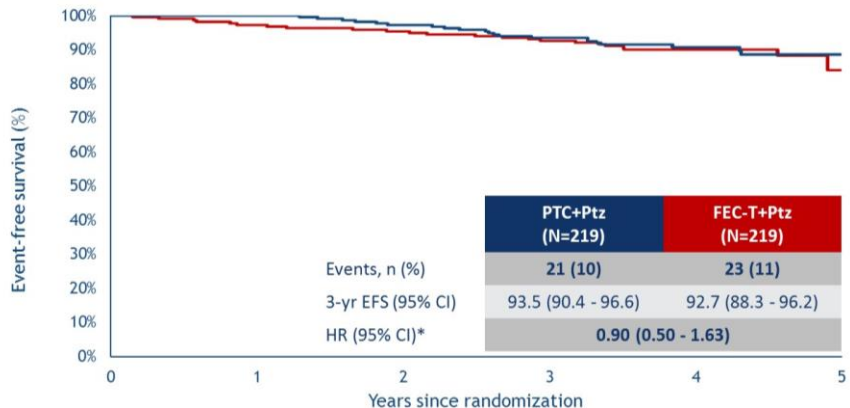


Fase 3 TRAIN-2

Omissão da antraciclina na doença HER2+?

ENDPOINTS SECUNDÁRIOS

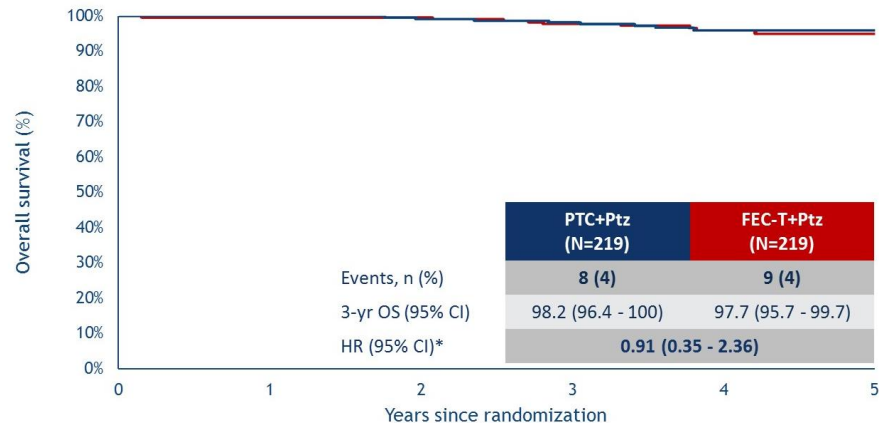
Event-free survival



No. at risk

	0	1	2	3	4	5
PTC+Ptz	219	219	212	203	106	19
FEC-T+Ptz	219	213	209	200	103	17

Overall survival



No. at risk

	0	1	2	3	4	5
PTC+Ptz	219	219	216	213	110	21
FEC-T+Ptz	219	218	218	211	111	20

Safety: cardiotoxicity

	PTC+Ptz (n=218) n (%)	FEC-T+Ptz (n=220*) n (%)	p-value
LVEF decrease $\geq 10\%$ <u>or</u> LVEF $< 50\%$	49 [#] (22%)	80 (36%)	0.0016
LVEF decrease $\geq 10\%$ <u>and</u> LVEF $< 50\%$	7 (3%)	17 (8%)	0.044

LVEF was measured every 3 months for 1 year

* one patient was allocated to PTC+Ptz but received neoadjuvant FEC-T+PTZ

one patient developed grade 2 LVEF decline during adjuvant treatment with anthracyclines

LVEF decline did not recover to normal during follow-up in about one third of the patients

PREOPERATIVE/ADJUVANT THERAPY REGIMENS^a

HER2-Positive

Preferred Regimens:

- Paclitaxel + trastuzumab^h
- TCH (docetaxel/carboplatin/trastuzumab)
- TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)
- If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab^j (category 1) ± pertuzumab.
- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.^{i,j} If node positive at initial staging, trastuzumab + pertuzumab (category 1)^k

Useful in Certain Circumstances:

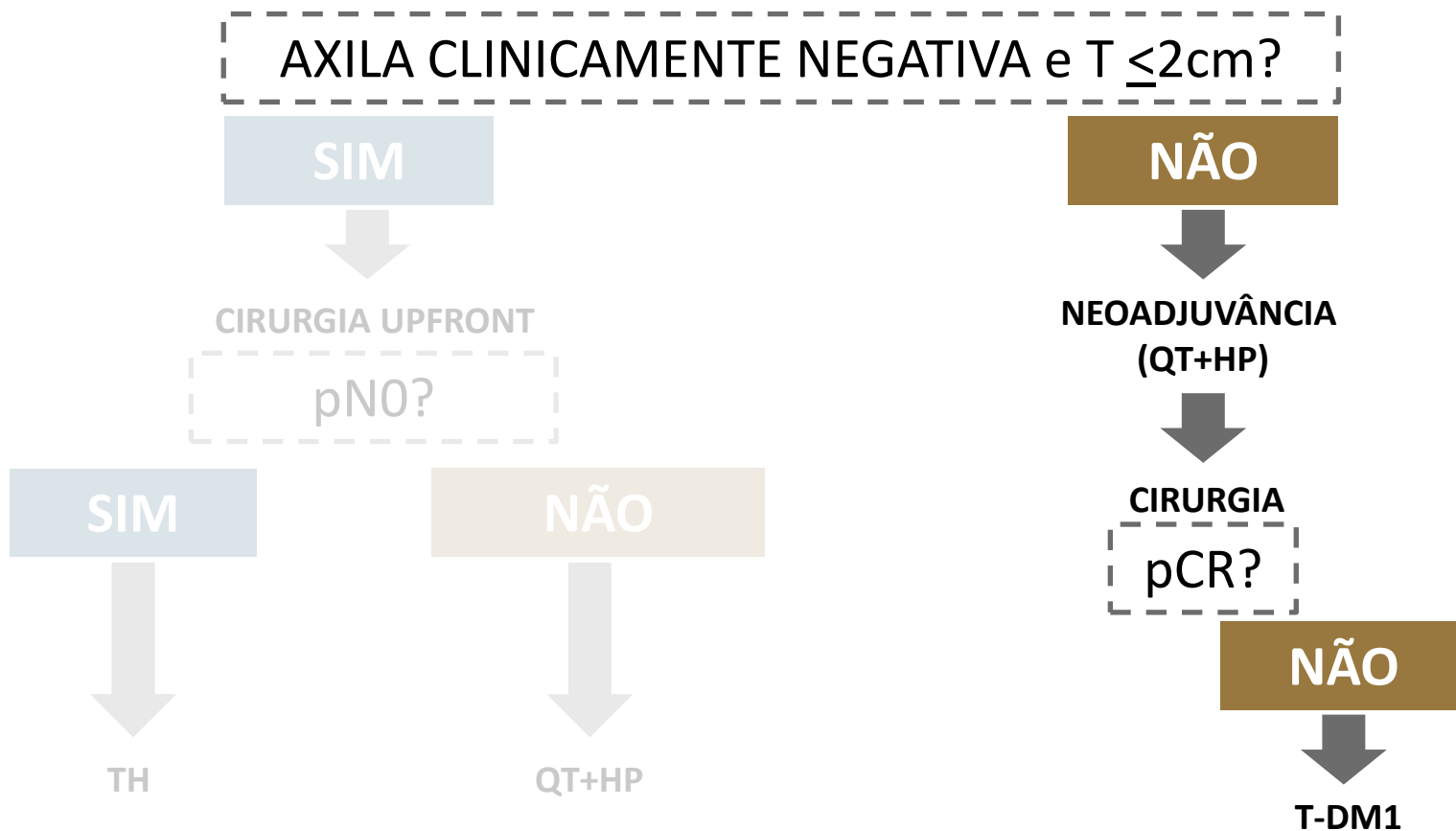
- Docetaxel + cyclophosphamide + trastuzumab
- AC followed by T^c + trastuzumab^j (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- AC followed by T^c + trastuzumab + pertuzumab^j (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)
- Neratinibⁱ (adjuvant setting only)
- Paclitaxel + trastuzumab + pertuzumab^j
- Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)

Other Recommended Regimens:

- AC followed by docetaxel^c + trastuzumab^j (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)
- AC followed by docetaxel^c + trastuzumab + pertuzumab^j (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

CÂNCER DE MAMA HER2-POSITIVO NÃO METASTÁTICO

Como conduzir em 2023?



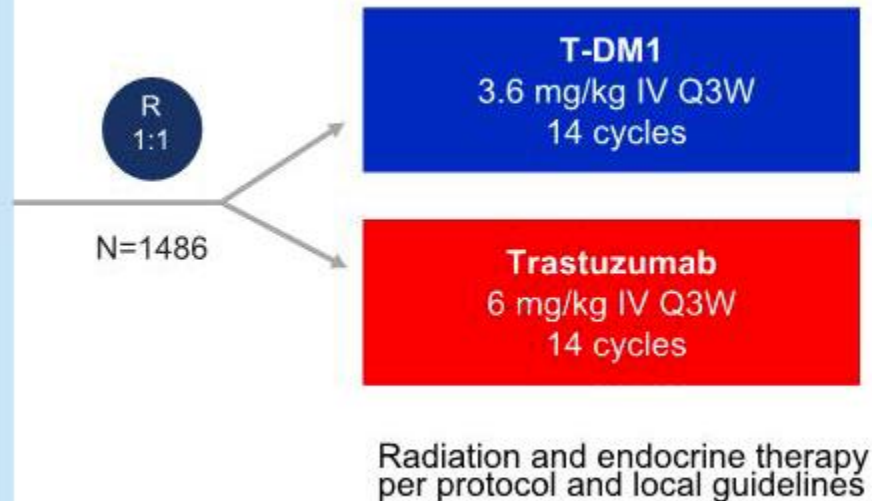
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- Downstaging axilar /redução das linfadenectomias
- Teste in vivo de agentes anti-neoplásicos e informação prognóstica
- **Seleção de pacientes para novas terapias com impacto em sobrevida**

FASE 3 KATHERINE

Desenho do estudo

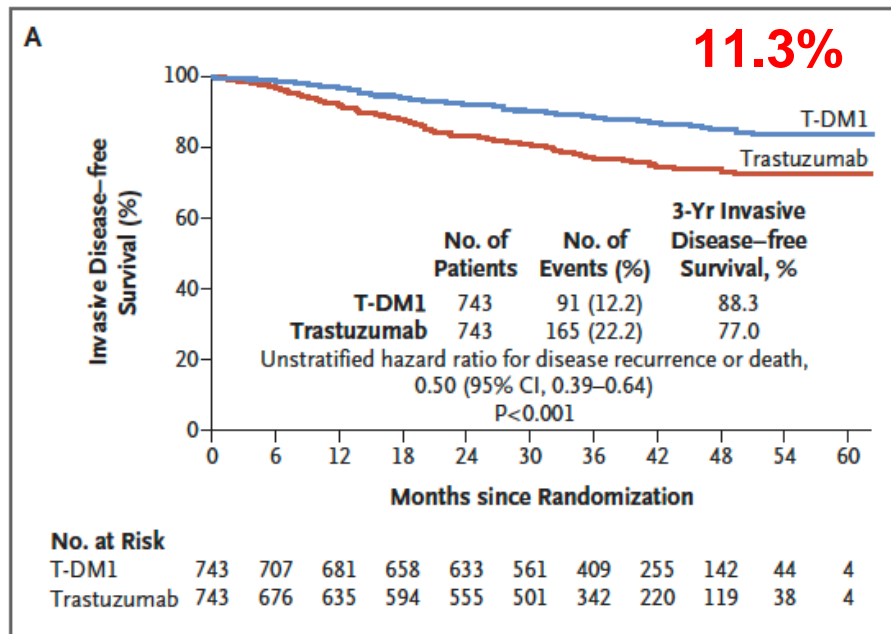
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
 - Minimum of 6 cycles of chemotherapy
 - Minimum of 9 weeks of taxane
 - Anthracyclines and alkylating agents allowed
 - All chemotherapy prior to surgery
 - Minimum of 9 weeks of trastuzumab
 - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



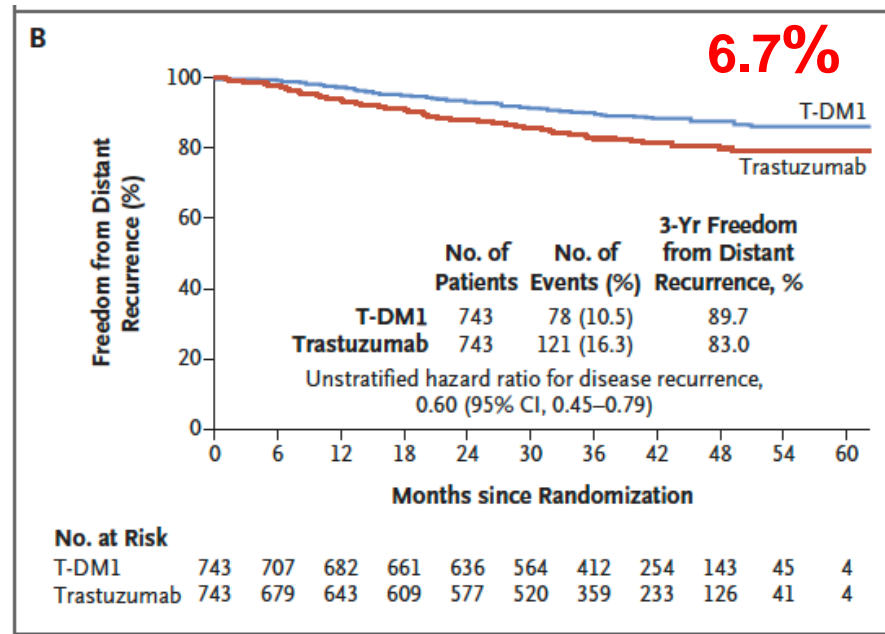
FASE 3 KATHERINE

Resultados: sobrevida

Sobrevida Livre de Doença Invasiva

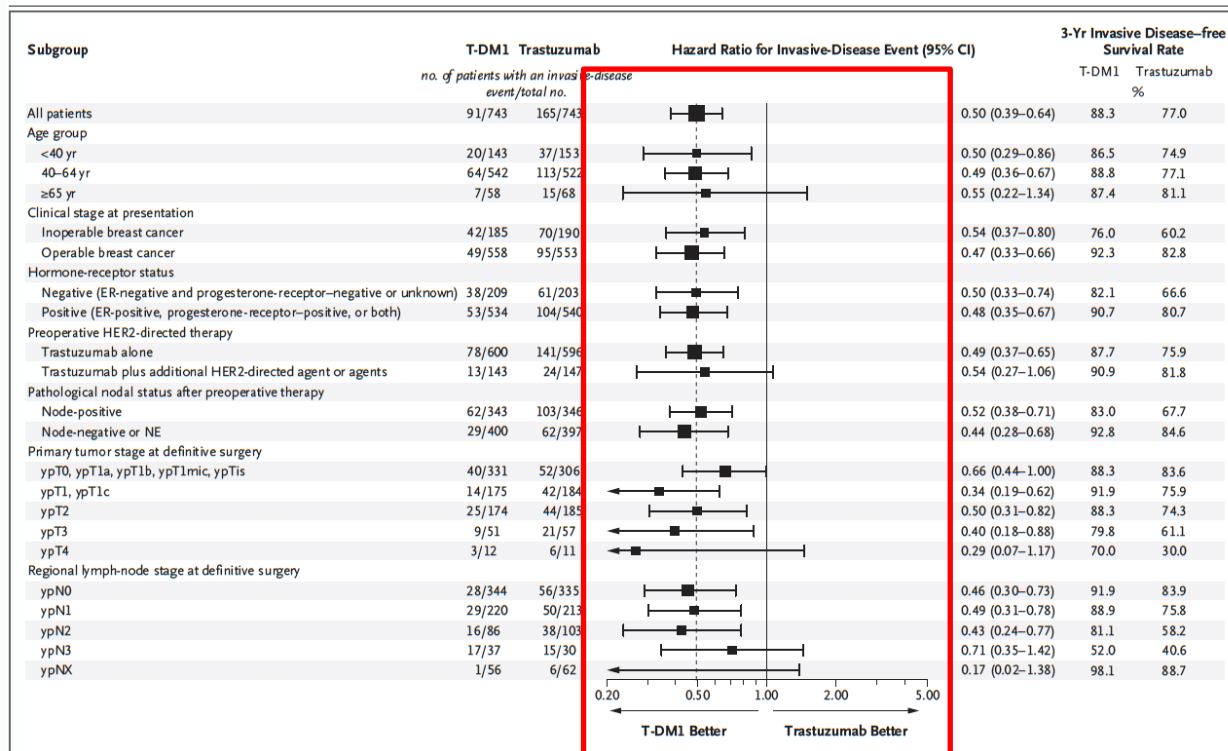


Sobrevida Livre de Recorrência à Distância



FASE 3 KATHERINE

IDFS por subgrupos

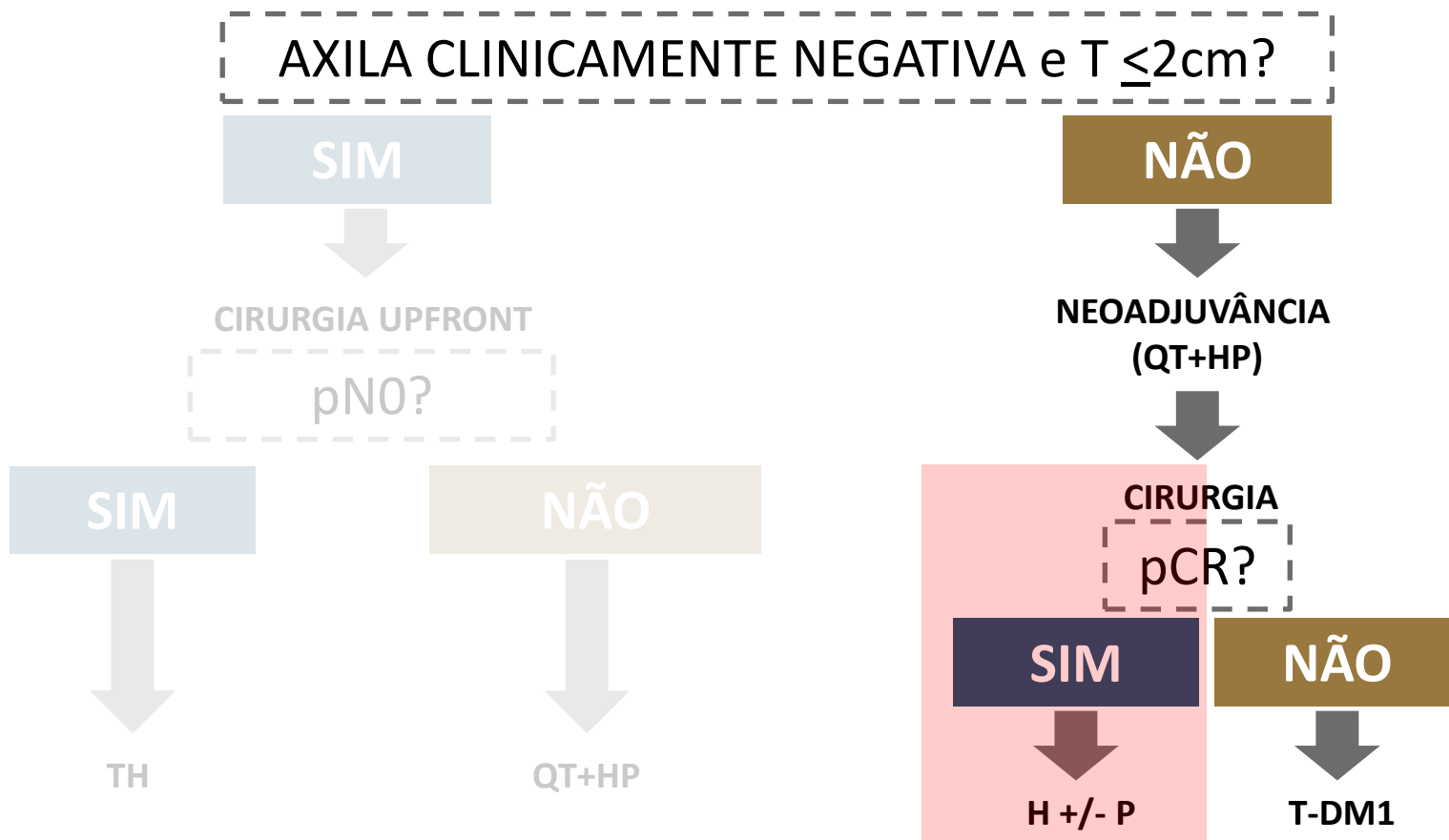


Benefício de T-DM1 foi mantido independentemente de:

- ✓ Regime de quimioterapia utilizado previamente
- ✓ Status de HER2 na peça cirúrgica
- ✓ Mutações de PIK3CA

CÂNCER DE MAMA HER2-POSITIVO NÃO METASTÁTICO

Como conduzir em 2023?



Pacientes que evoluem com pCR ainda estão sob risco de recorrência!

Estudo	Subtipo	N (pCR)	% recorrência	Tempo de seguimento
Retrospective single center Belgium ¹	HER2+ e TN	243	9,1% (8,2% à distância)	57m
GBG – polled analysis of GeparTrio, GeparQuattro, GeparQuinto, GeparSixto and GeparSepto ²	Todos os subtipos	2.188	13,2% (9% à distância)	59m
Neosphere ³	HER2+	94	15,0%	60m

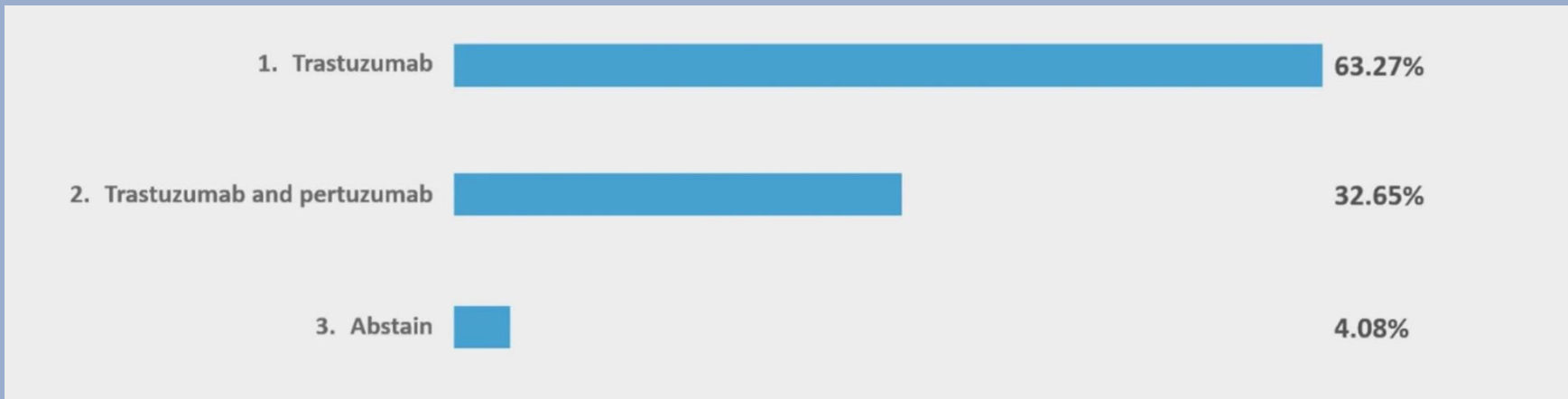
1. Borremans et al. Cancer Res (2019) 79 (4_Supplement): P1-15-04

2. Huober et al. Cancer Res (2019) 79 (4_Supplement): P2-08-01

3. Gianni et al. Lancet Oncol. 2016 Jun;17(6):791-800

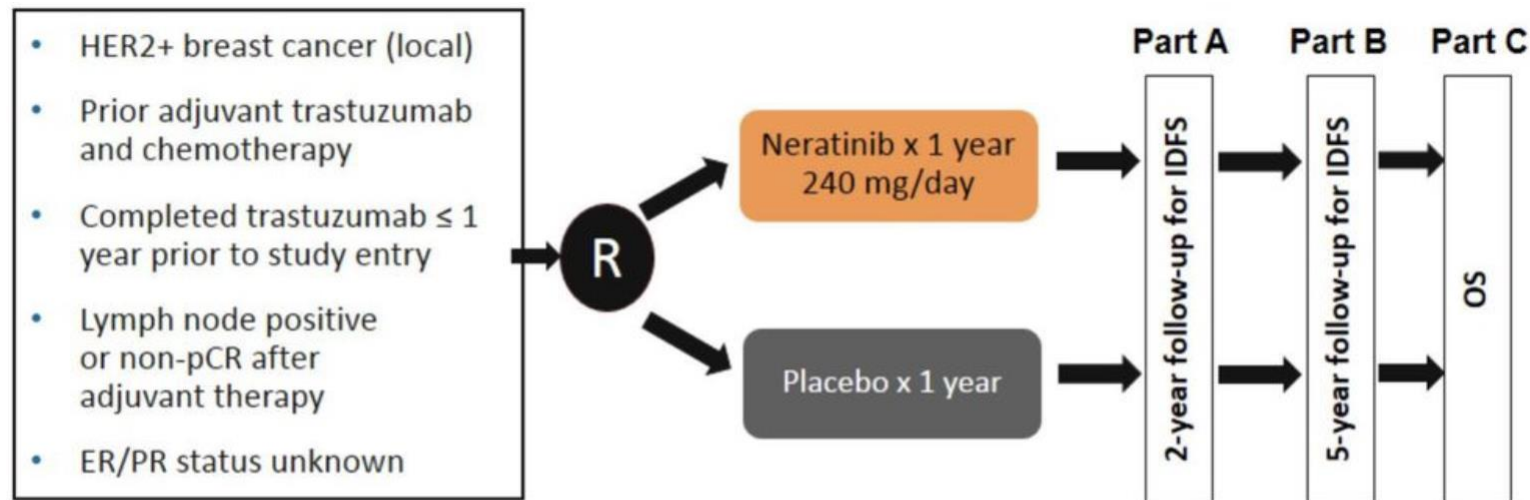
ALERTA St. Gallen 2023:

Qual é o tratamento adjuvante mais apropriado para pacientes com axila clinicamente negativa, que receberam TCHP neoadjuvante e evoluíram com pCR?



FASE 3 EXTENET

NERATINIBE COMO TERAPIA ESTENDIDA



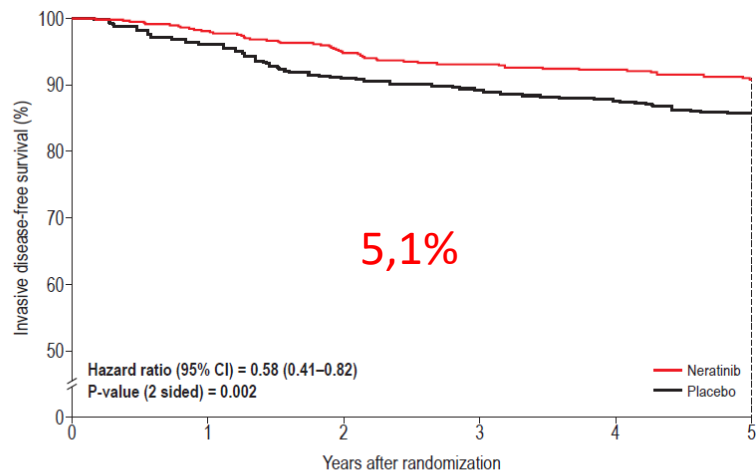
- Primary analysis: IDFS in ITT population (n = 2840)
- IDFS at 2 years: hazard ratio = 0.67 (0.50, 0.91); $P = .0091$
- HR positive (n = 1631, 57.4%); hazard ratio = 0.51; $P = .0013$
- Centrally confirmed HER2-positive 60% (n = 1463; 51%); hazard ratio = 0.51; $P = .002$

FASE 3 EXTENET

NERATINIBE COMO TERAPIA ESTENDIDA

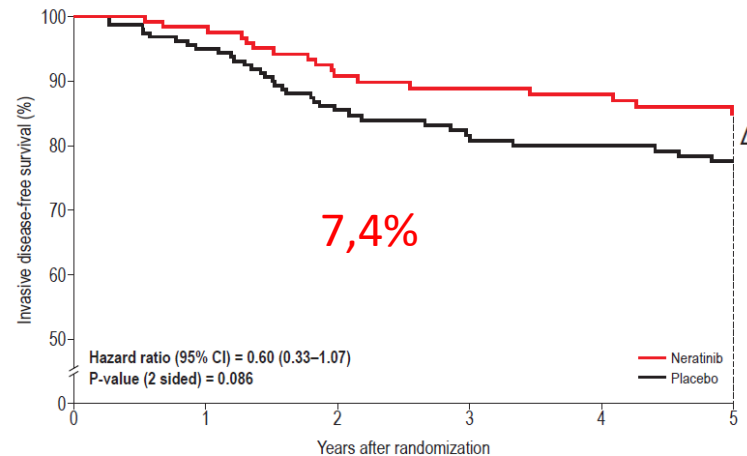
*** Diarréia G3 40%**

IDFS 5 anos para RE+/≤1ano



No. at risk	0	1	2	3	4	5					
Neratinib	670	620	599	577	523	469	465	460	457	448	421
Placebo	664	634	609	583	535	481	471	462	458	450	431

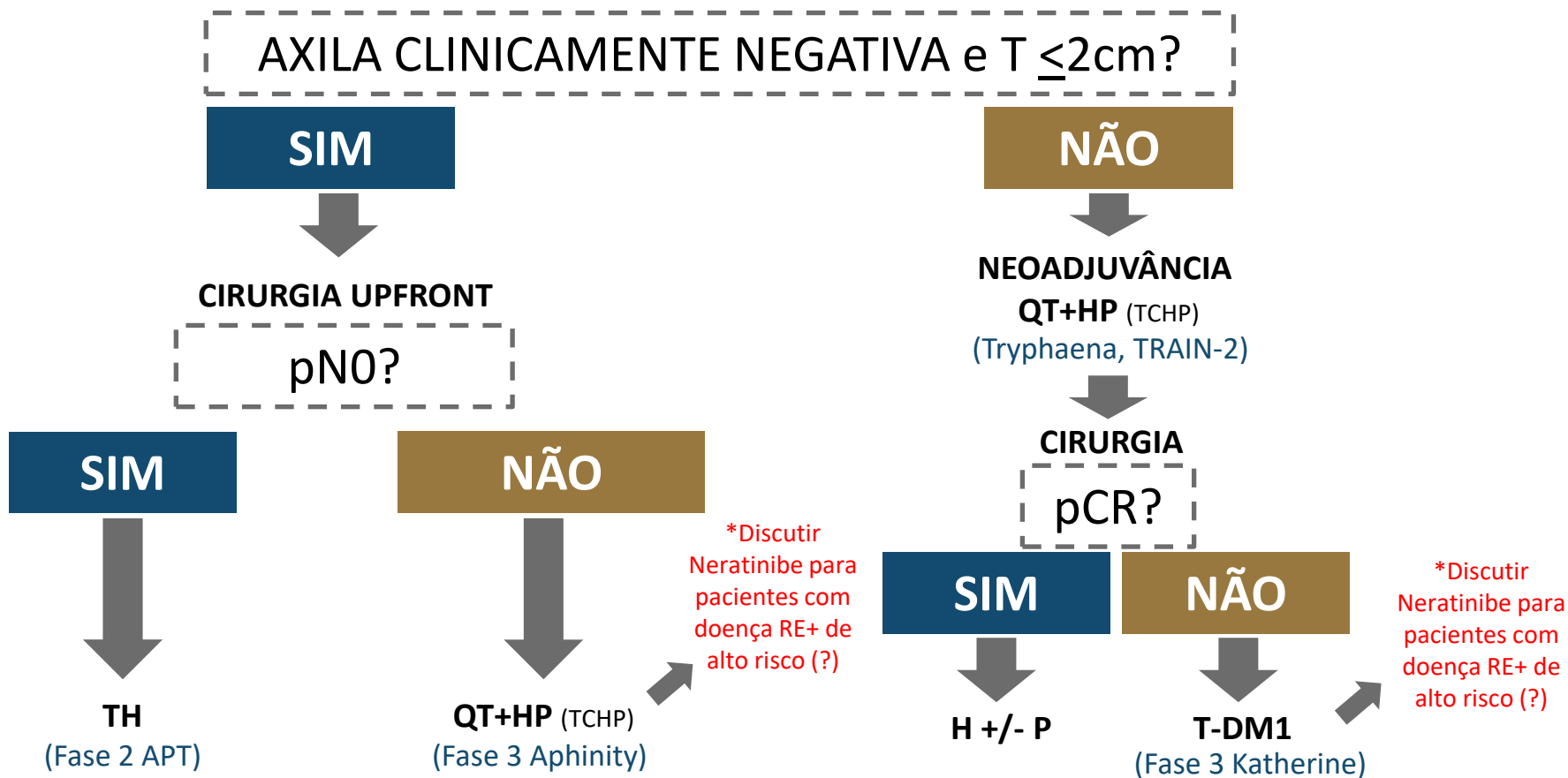
IDFS 5 anos para RE+/≤1ano (e sem pCR)



No. at risk	0	1	2	3	4	5					
Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

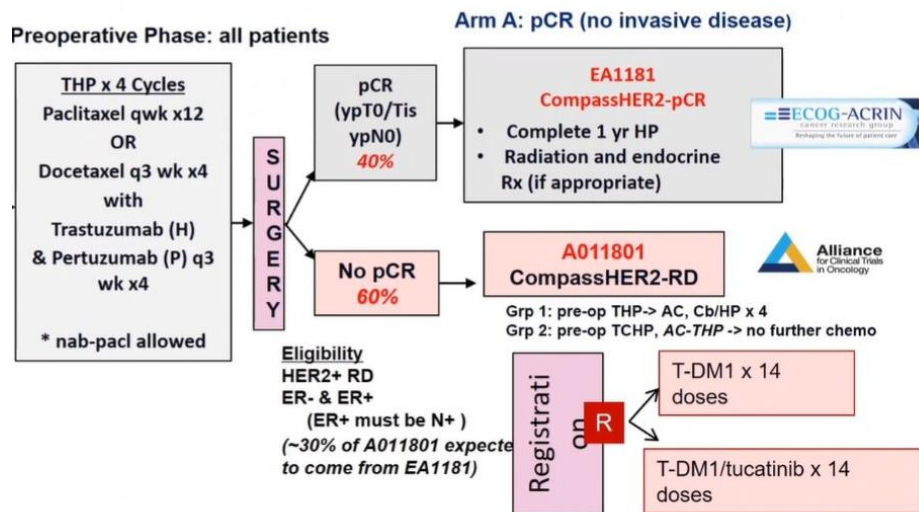
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Como conduzir em 2023?

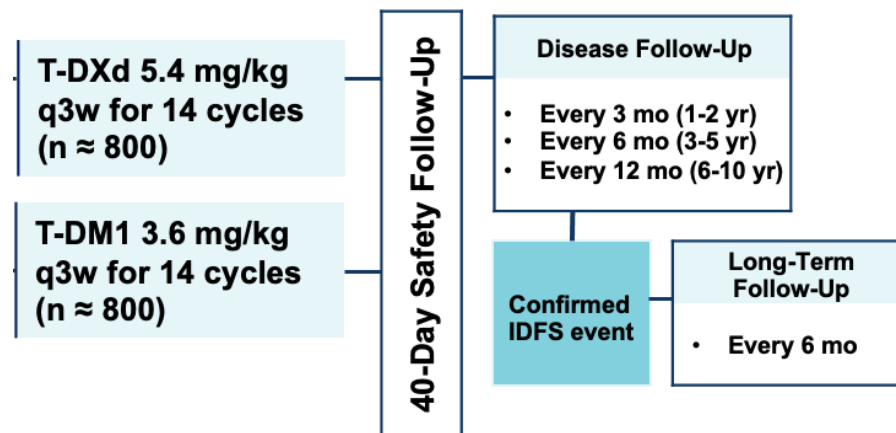


Como melhorar os resultados em pacientes que não atingem pCR?

Fase 3 Compass-HER2 ¹



Fase 3 Destiny Breast 05 ²



1. <https://clinicaltrials.gov/ct2/show/NCT04266249>

2. <https://clinicaltrials.gov/ct2/show/NCT04622319>

Obrigado!

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RADIATION
ONCOLOGY
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APOIO

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REALIZAÇÃO

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DE ESTUDOS EM LANCER
DE MAMA

GERENCIAMENTO
& PRODUÇÃO

RV+