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GRUPO BRASILEIRO
DE ESTUDOS EM CÂNCER
DE MAMA

GERENCIAMENTO
E PRODUÇÃO

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ASSOCIAÇÃO BRASILEIRA DE RÁDIO

Avanços no tratamento do câncer de mama metastático HER2-low

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Grupo Brasileiro de Estudos em Câncer de Mama

Universidade Federal do Rio Grande do Sul

Conflitos de interesse

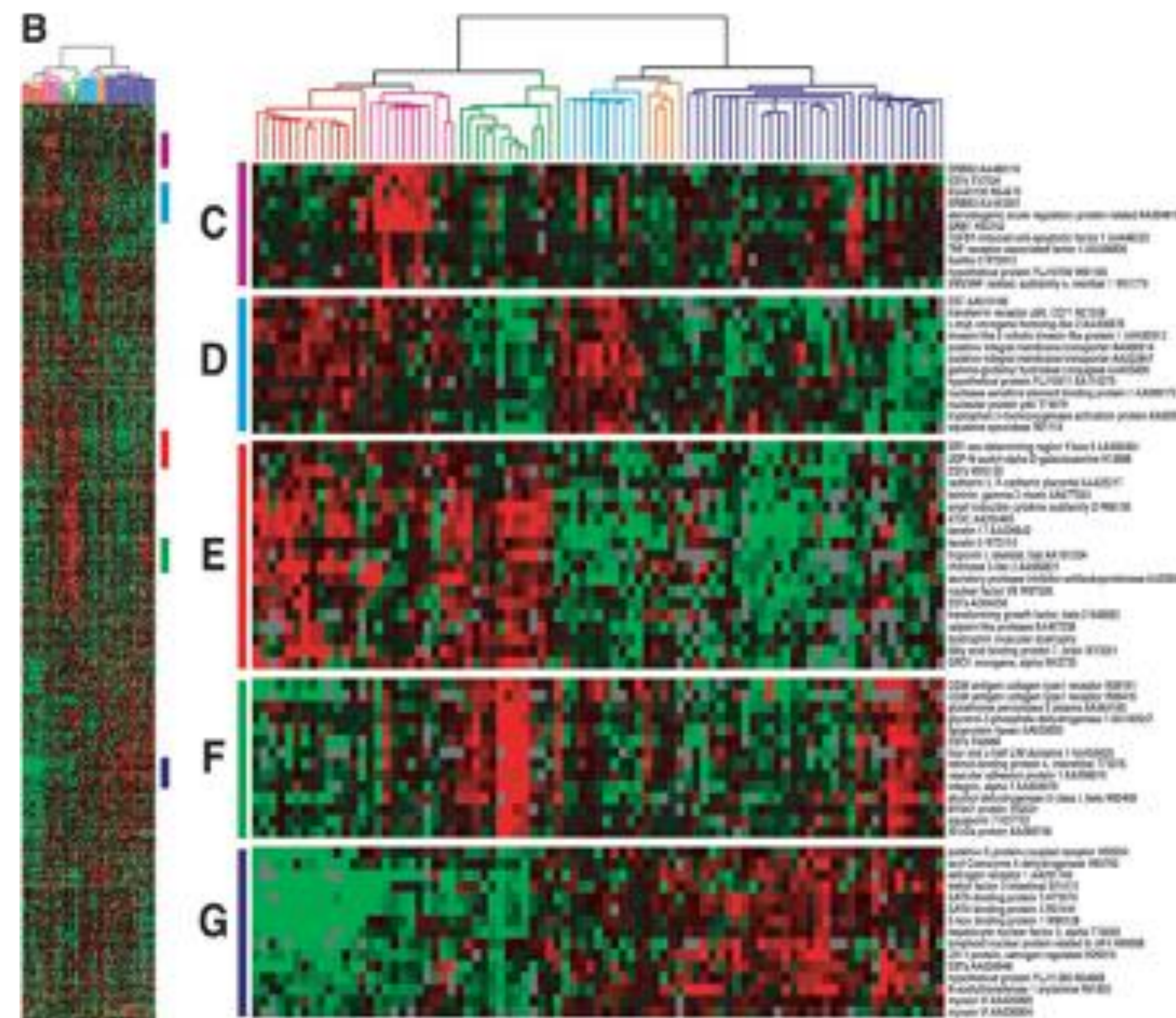
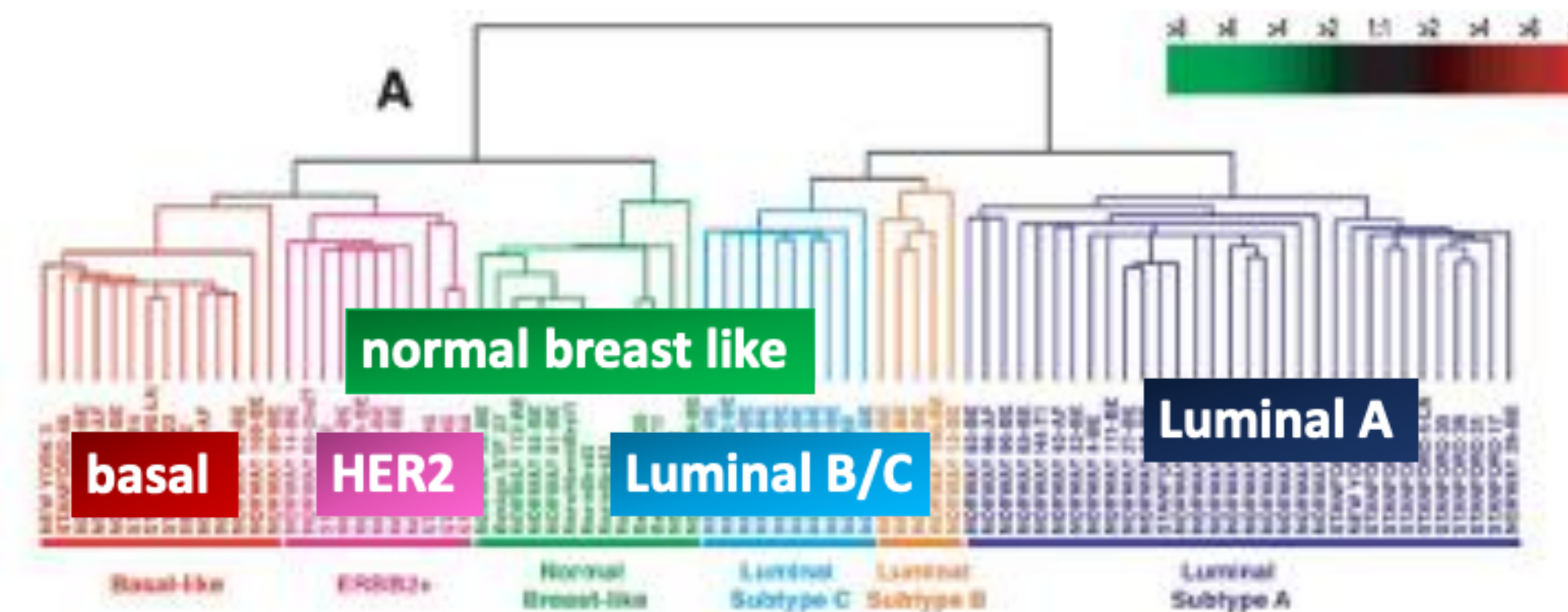
De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina e RDC 96/08 da ANVISA, declaro:

Consultoria: Roche, Novartis, AstraZeneca, Lilly, GSK, Sanofi, Libbs, Eisai, Pfizer, DrReddy's, Amgen, Teva, Zodiac, United Medical, MSD, Daiichi Sankyo

Participação em advisory boards: Roche, Novartis, Pfizer, AstraZeneca, Lilly, Zodiac, Teva

Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão.

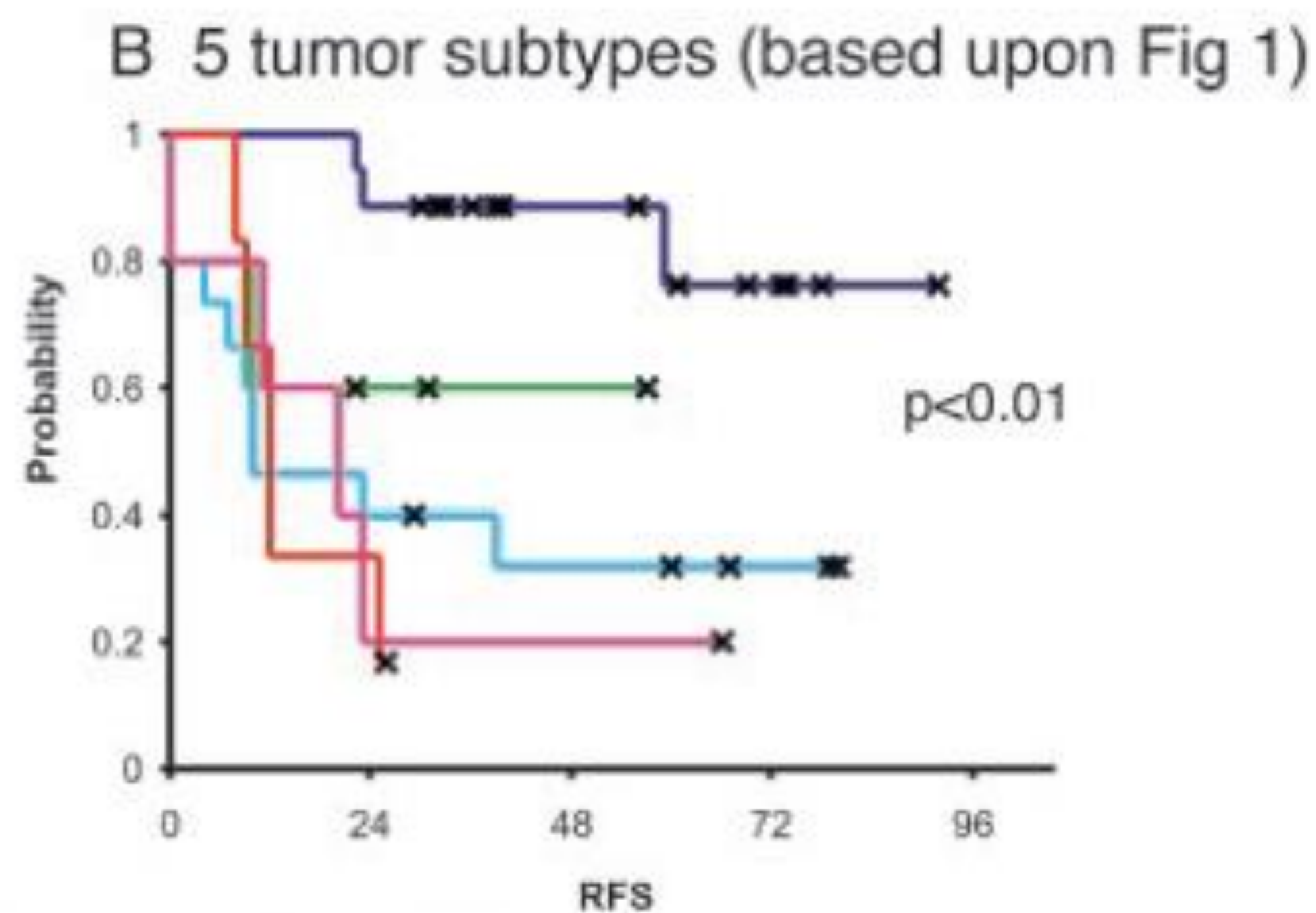
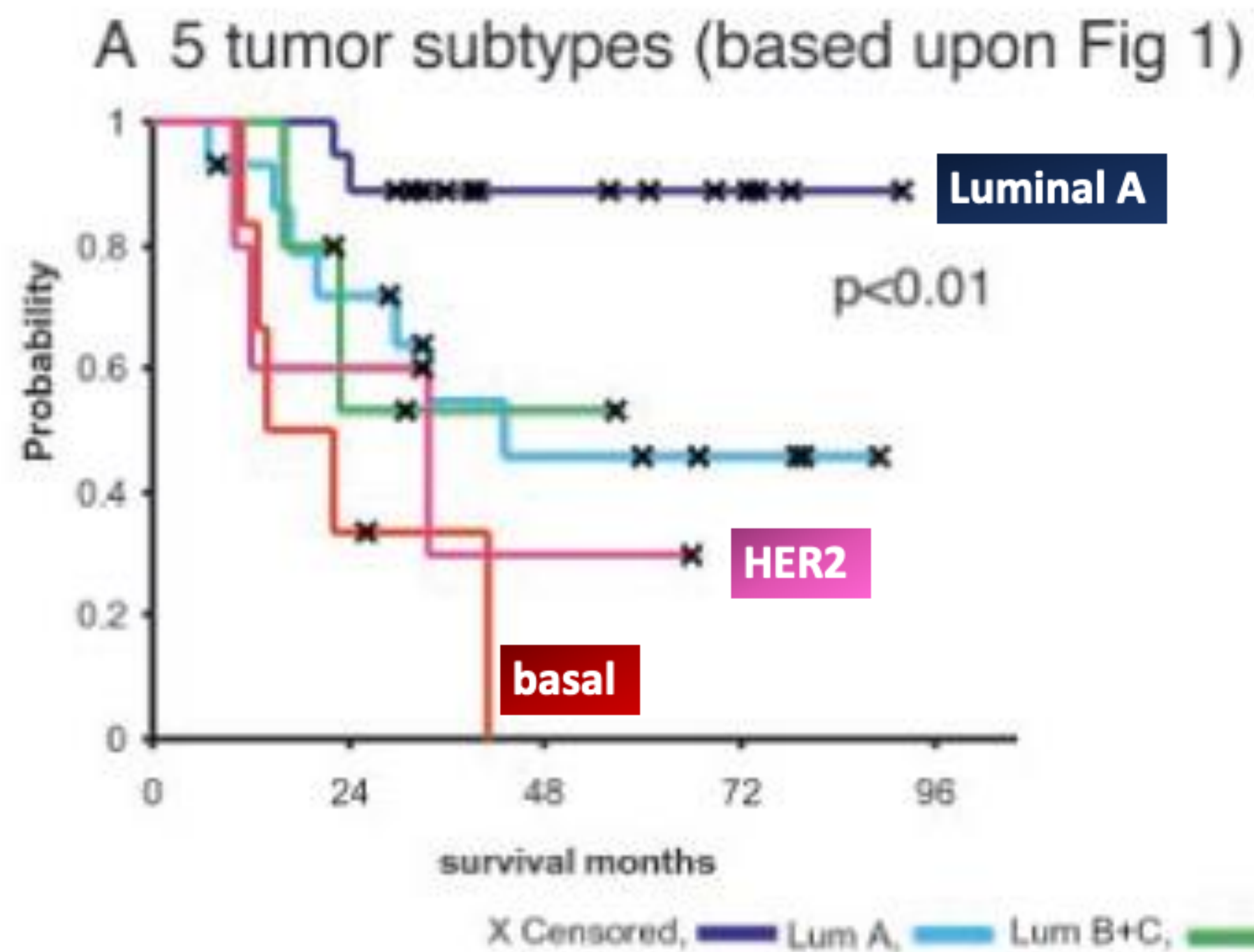
Subtipos



Subtipos biológicos são prognósticos

Sorlie T, Perou CM et al. PNAS 2001;98:10869

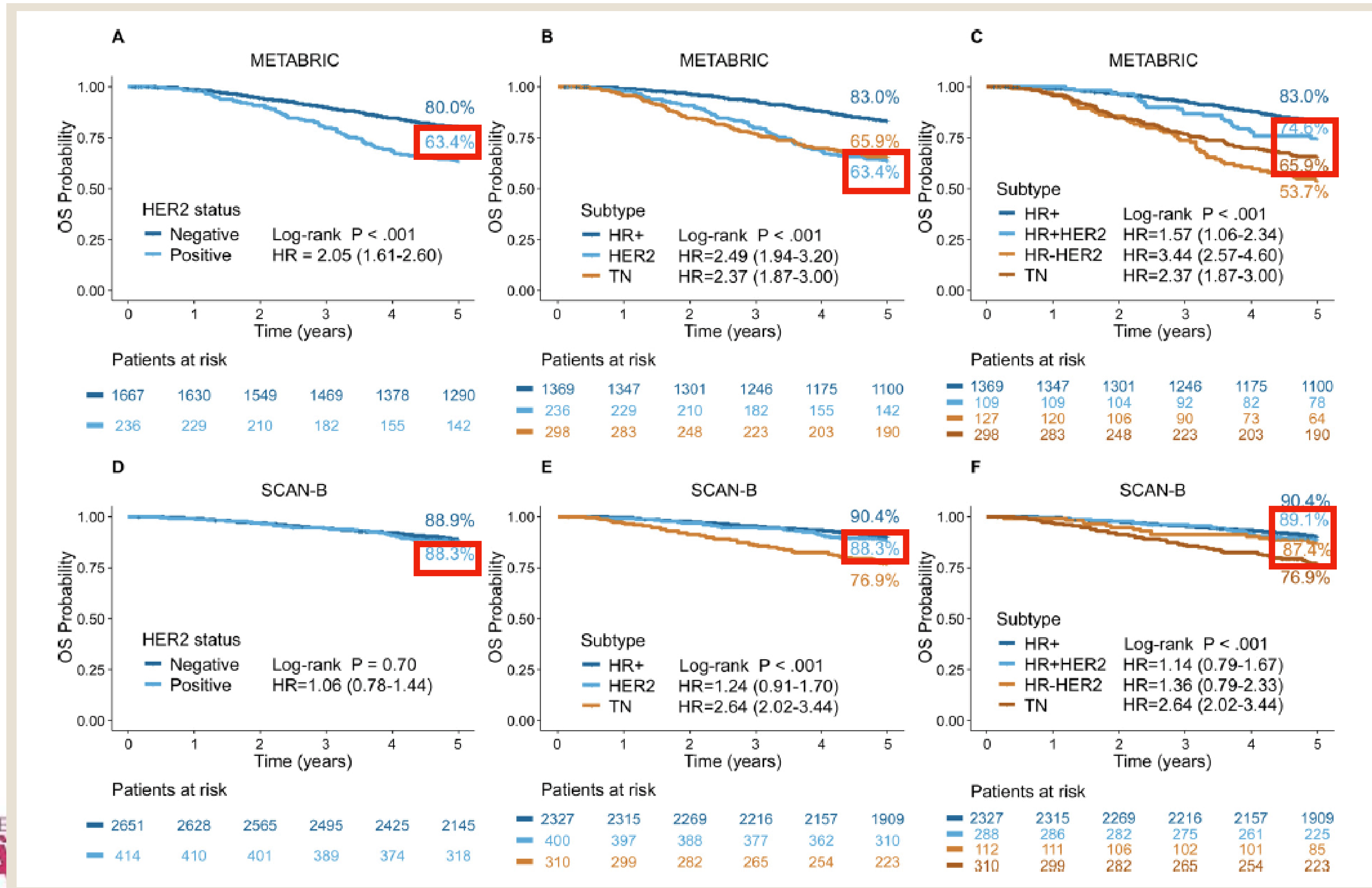
Prognóstico do CA mama



Subtipos biológicos são preditivos de resposta

Sorlie T, Perou CM et al. PNAS 2001;98:10869

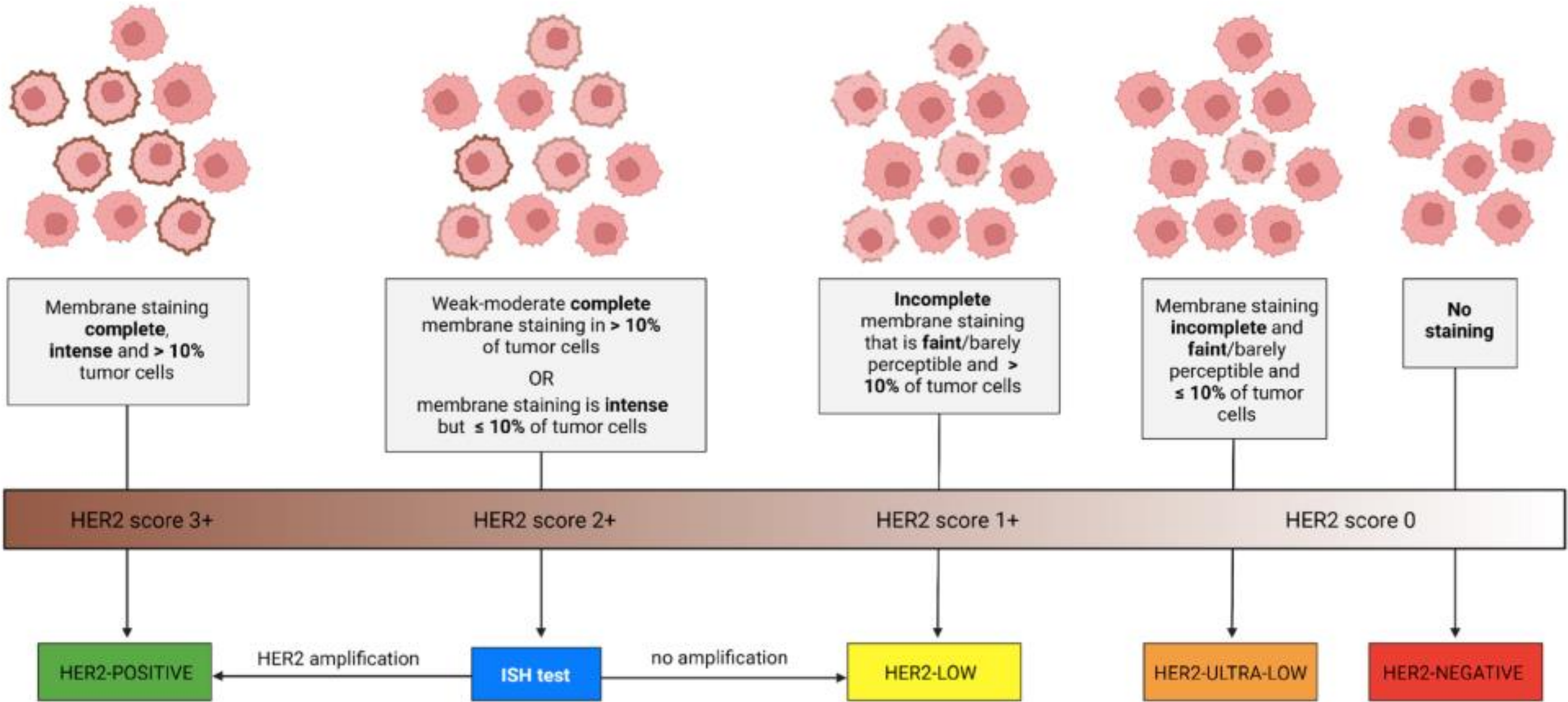
Prognóstico do CA mama antes e após bloqueio HER2



Before HER2-blockade

After HER2-blockade

Classificação da doença HER2



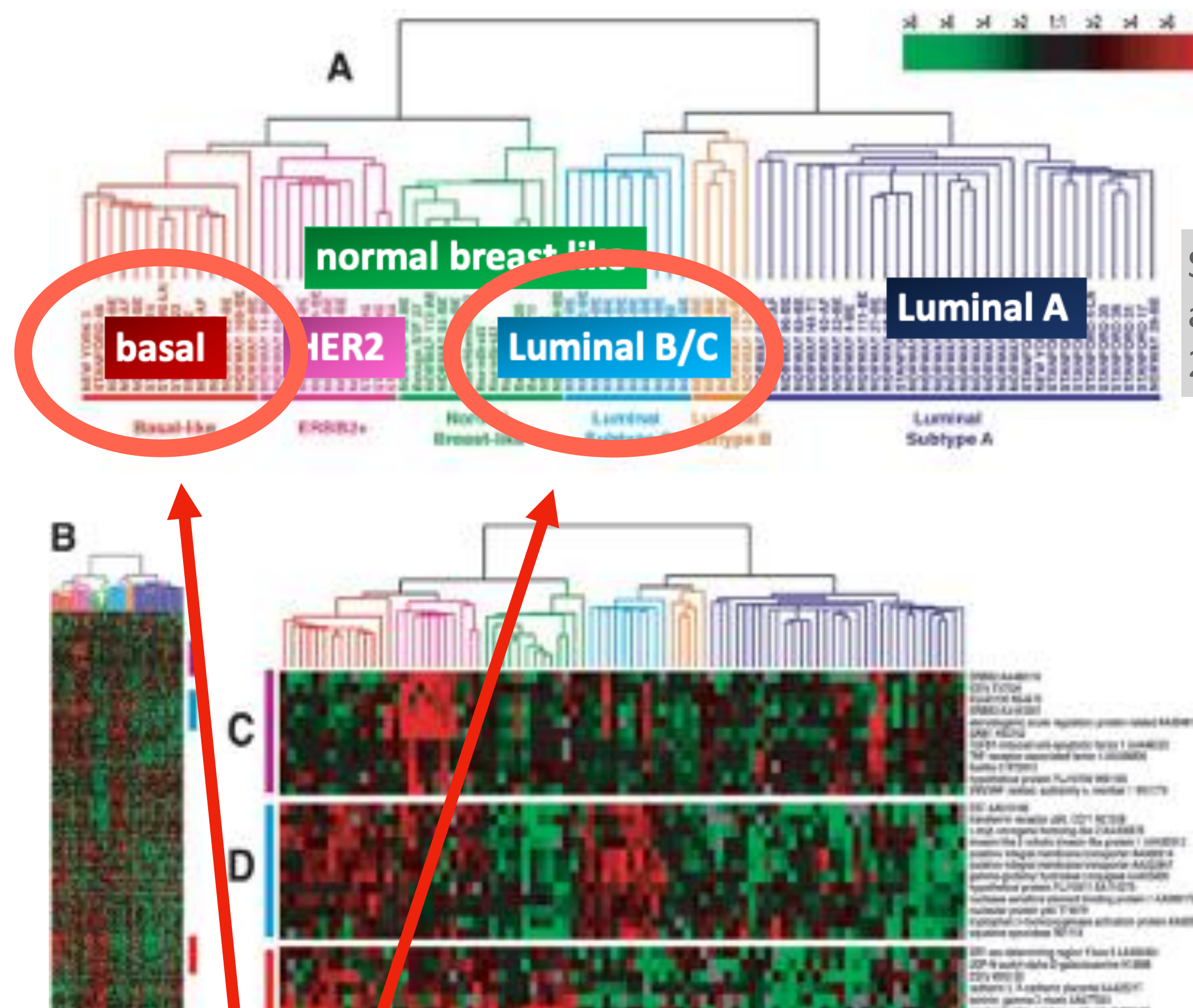
Potentially expanded spectrum of HER2 positivity

**40-50% dos tumores invasivos de mama
tem expressão baixa de HER2 (HER2 low):**

IHC 1+

IHC 2+ com ISH-

Subtipos



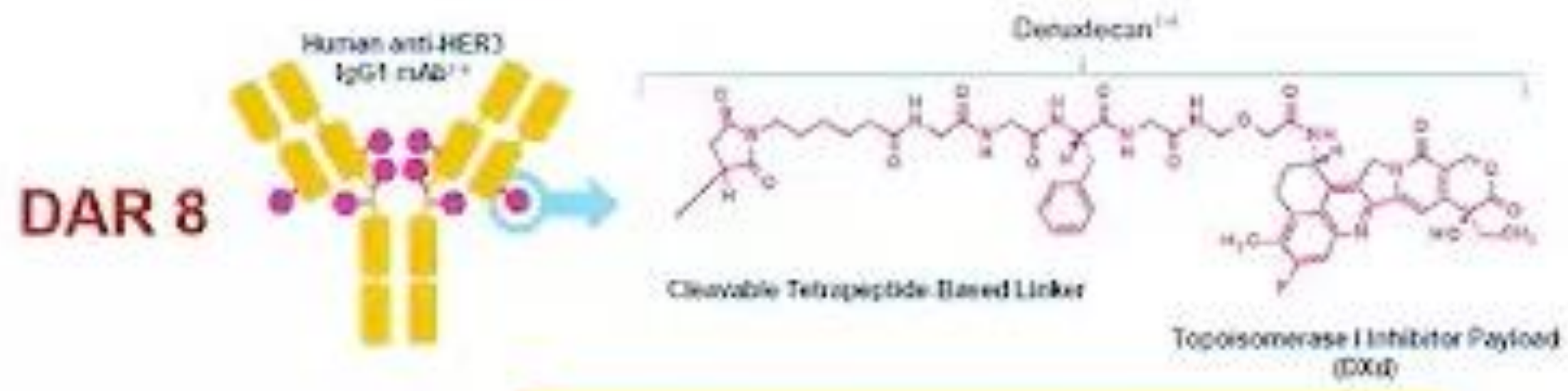
Sorlie T, Perou CM et al. PNAS 2001;98:10869

Table 1. HER2 Status With Immunohistochemistry and Fluorescence In Situ Hybridization (FISH) in 2590 Cases^a

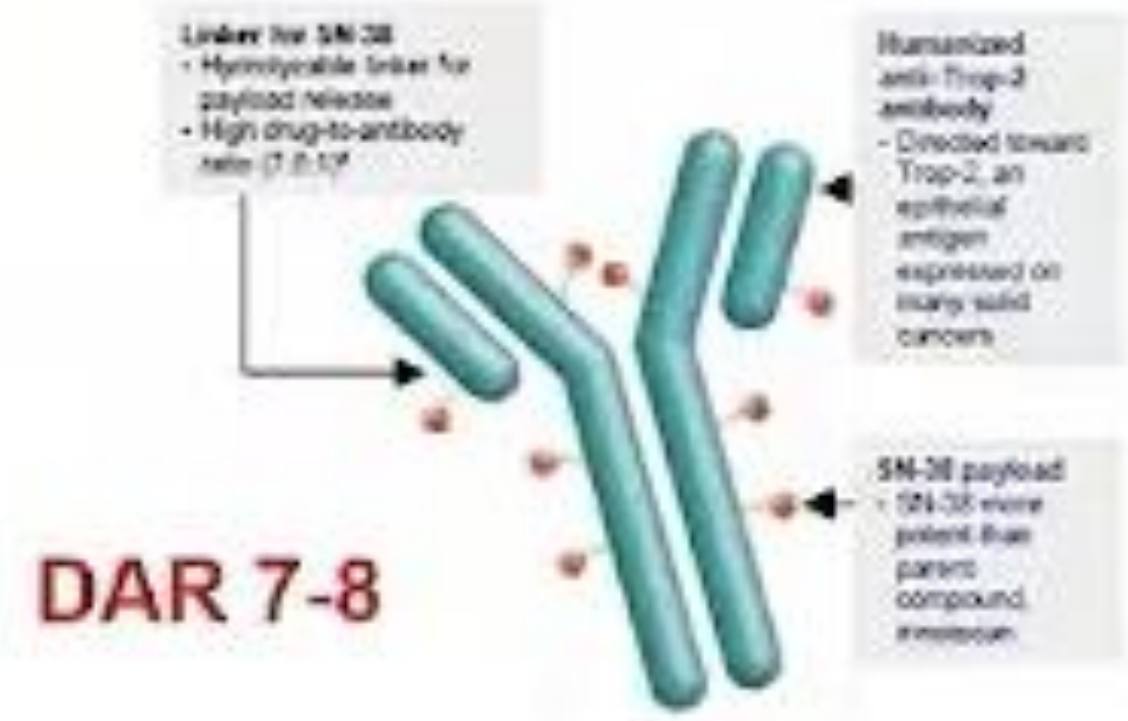
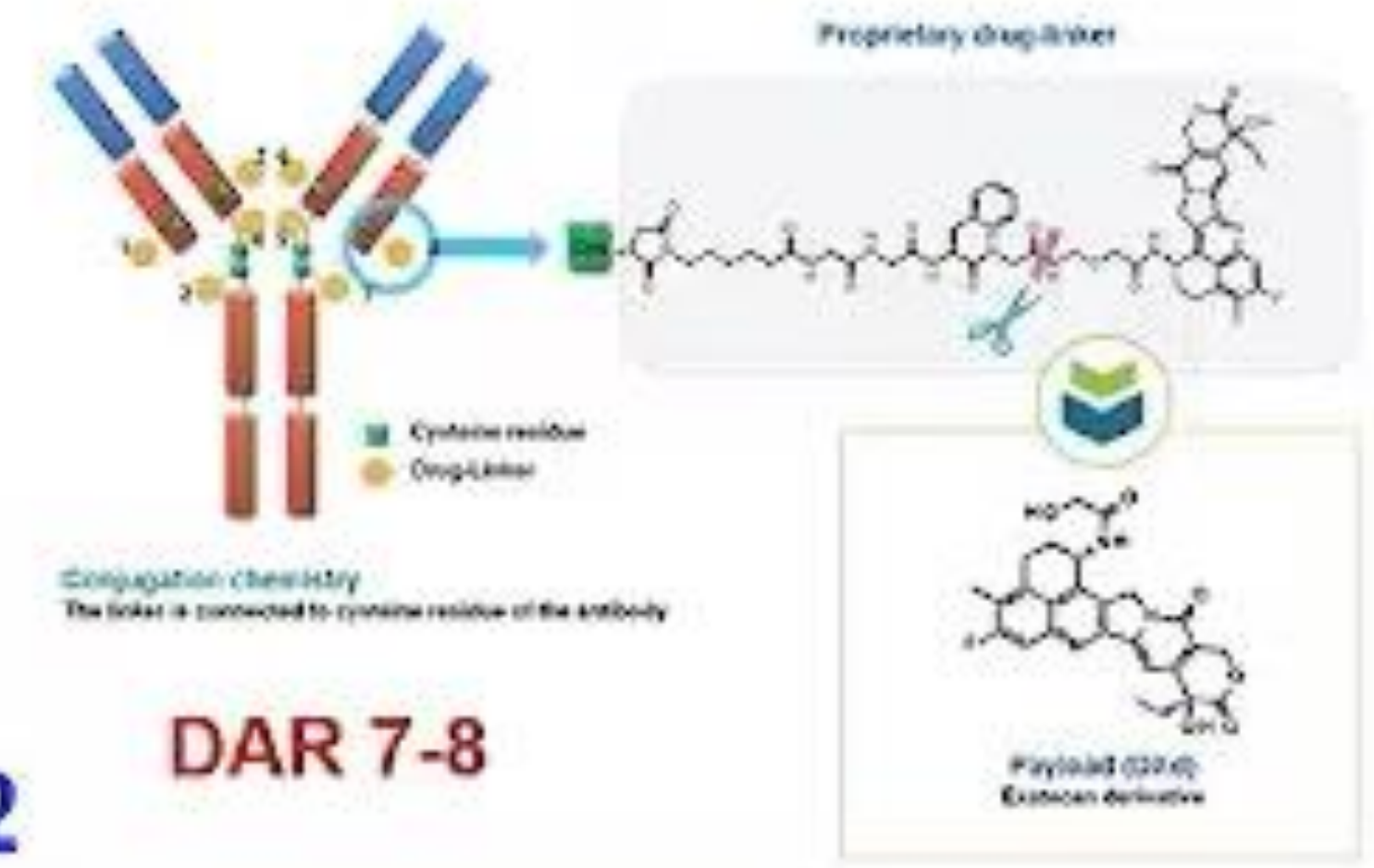
FISH	HER2/ <i>neu</i> Immunohistochemistry				Total
	0	1+	2+	3+	
Positive	5 (0.2)	21 (0.8)	63 (2.4)	197 (7.6)	286 (11.0)
Equivocal	10 (0.4)	7 (0.3)	16 (0.6)	5 (0.2)	38 (1.5)
Negative	850 (32.8)	815 (31.5)	554 (21.4)	47 (1.8)	2266 (87.5)
Total	865 (33.4)	843 (32.5)	633 (24.4)	249 (9.6)	2590

^a Data are expressed as number of cases (percentage of total).

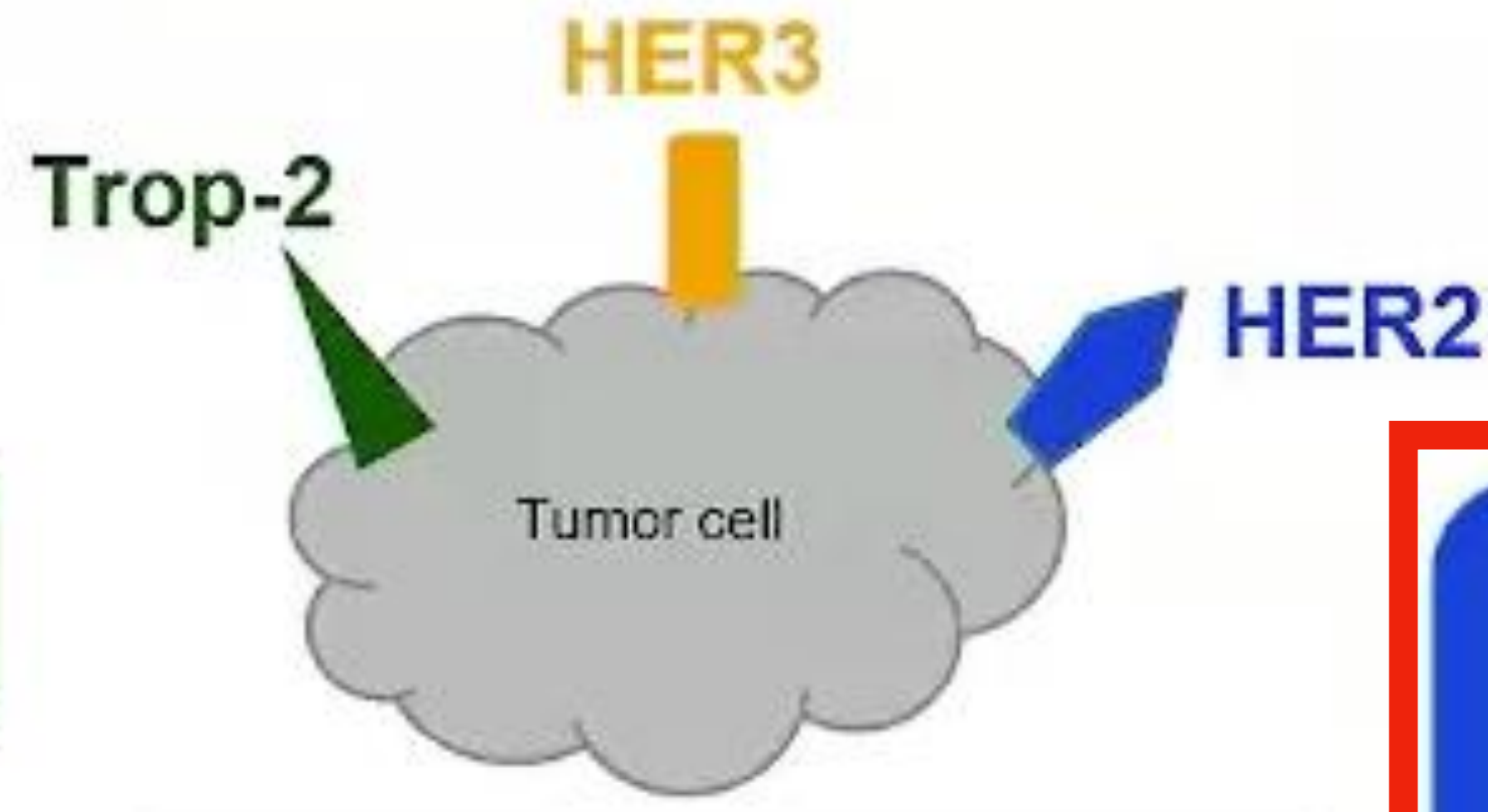
Conjugados droga-anticorpo (ADCs)



Patritumab deruxtecan
HER3-DXd Phase 1-2
I Krop



Sacituzumab govitecan
TROPICS in HR+ HER2- MBC
H Rugo



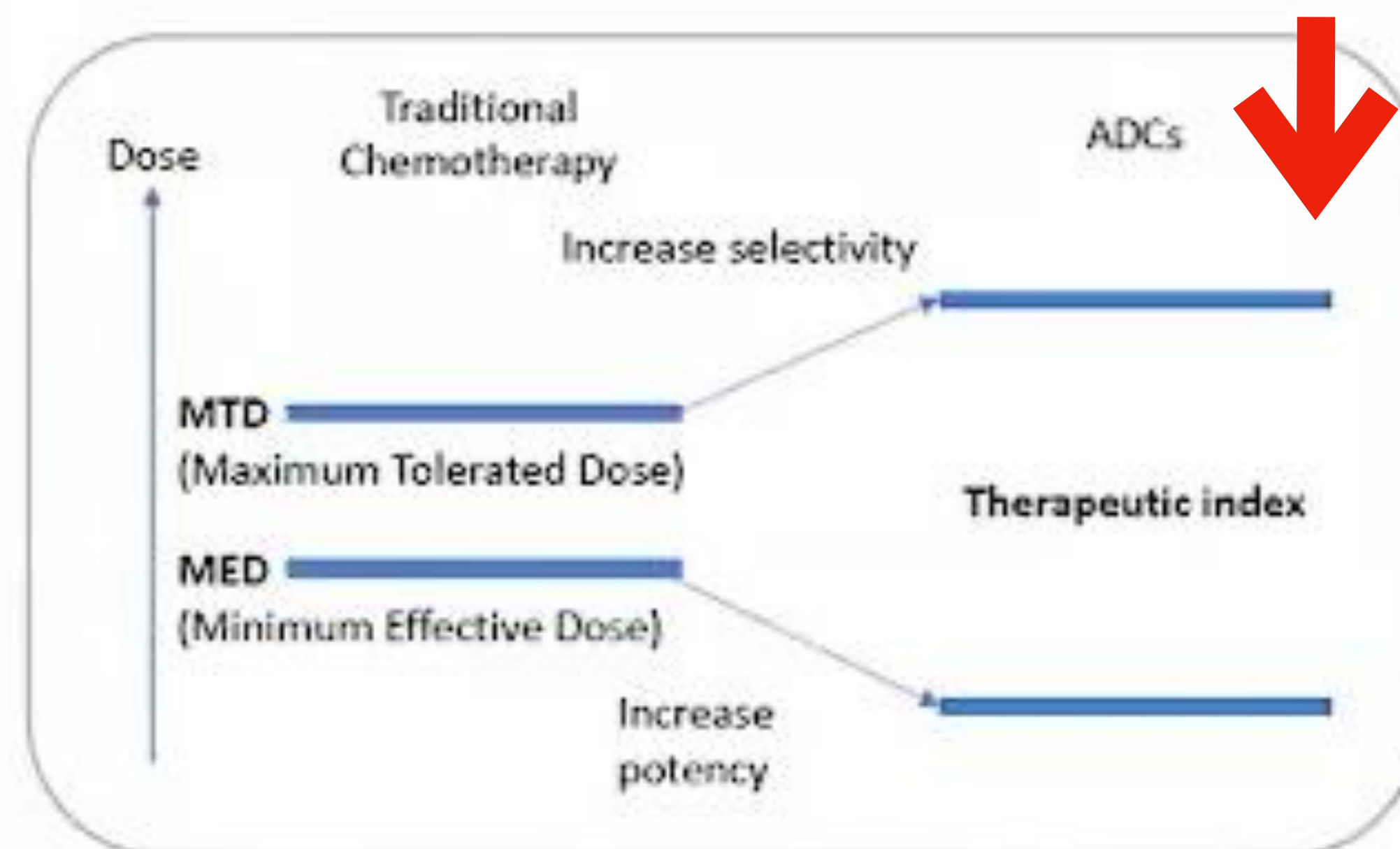
Trastuzumab Deruxtecan T-DXd

- Destiny-Breast03 in HER2+ MBC update safety *E Hamilton*
- Destiny-Breast04 in HER2 low *S Modi Plenary session*

ADCs were designed to address limitations of cytotoxic chemotherapy

Limitations of cytotoxic therapy

- Lack of tumor specificity
- Dose-limiting toxicity via systemic exposure of normal cells to cytotoxic agents
- Narrow therapeutic index



ADCs were designed to have an expanded therapeutic index:
Efficient and specific drug delivery to antigen-expressing tumor cells

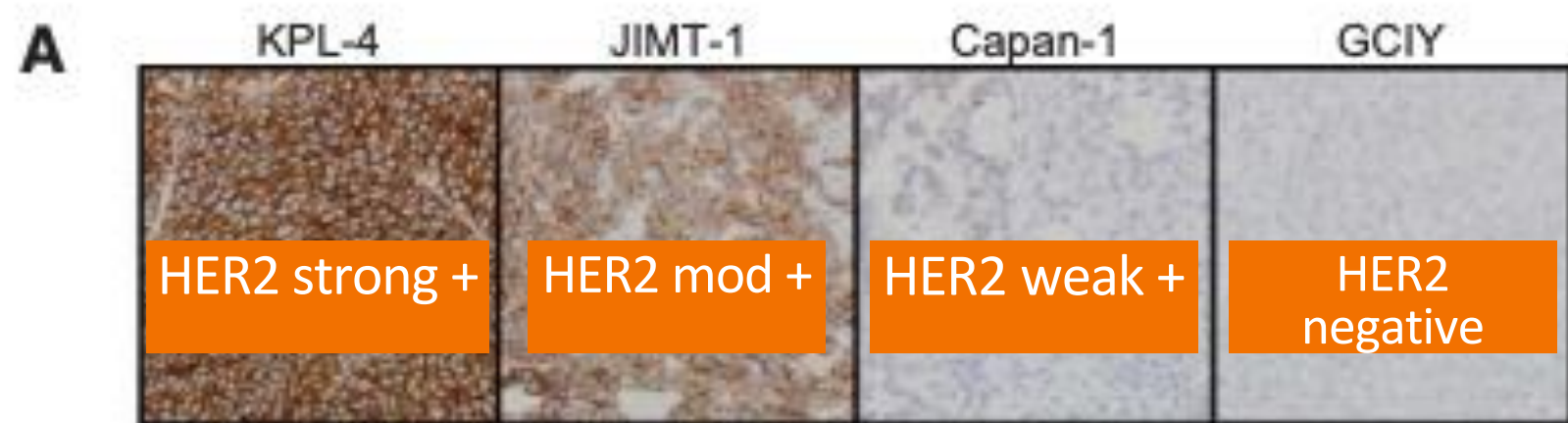


1913: Paul Ehrlich described the concept of a « magic bullet » and drug targeting

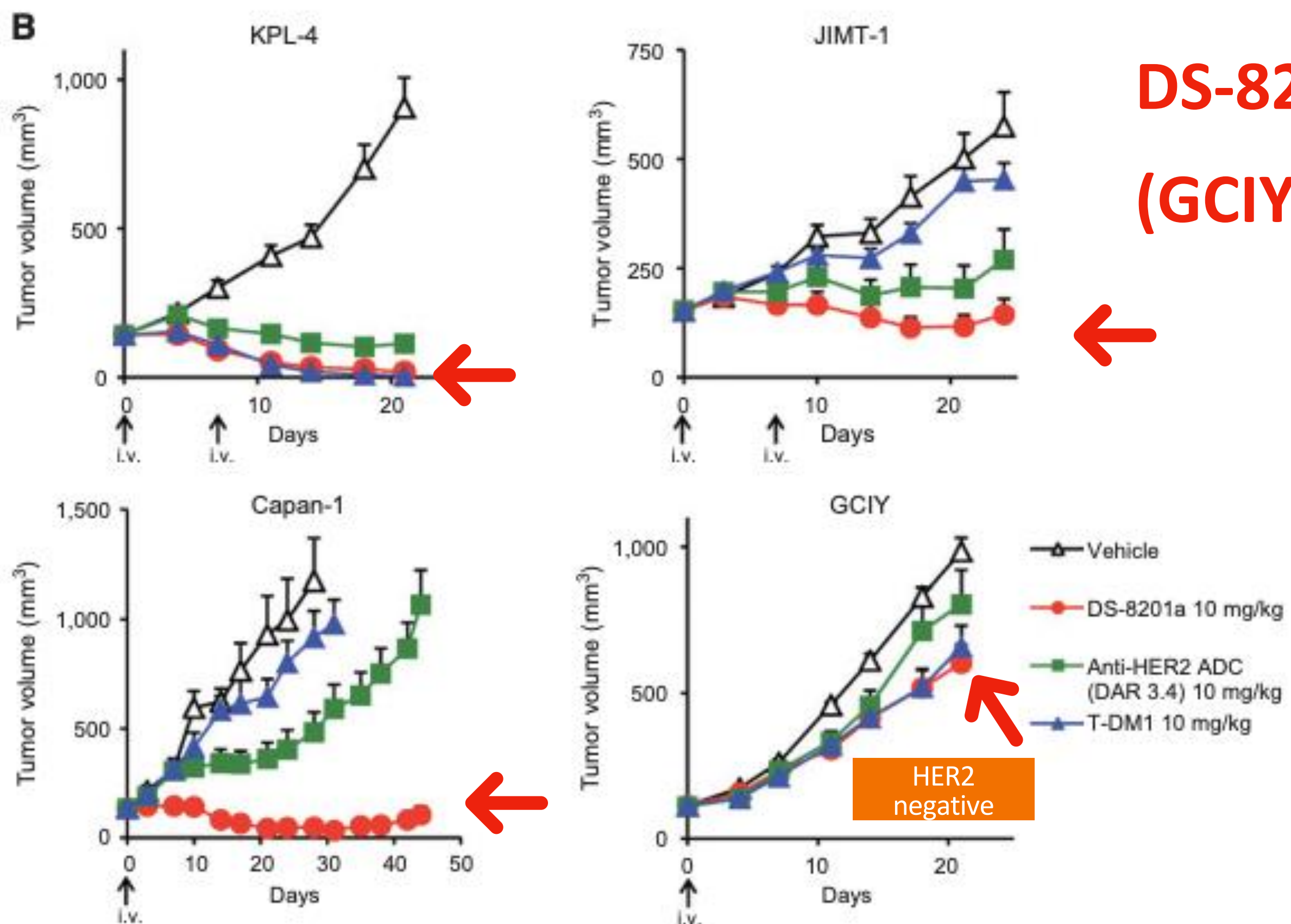
Lo Russo PM et al. Clin Cancer Res 2011, Nakada et al. Chem Pharm Bull 2019

HER2-low e resposta a ADC

DS-8201a (trastuzumabe deruxtecan)



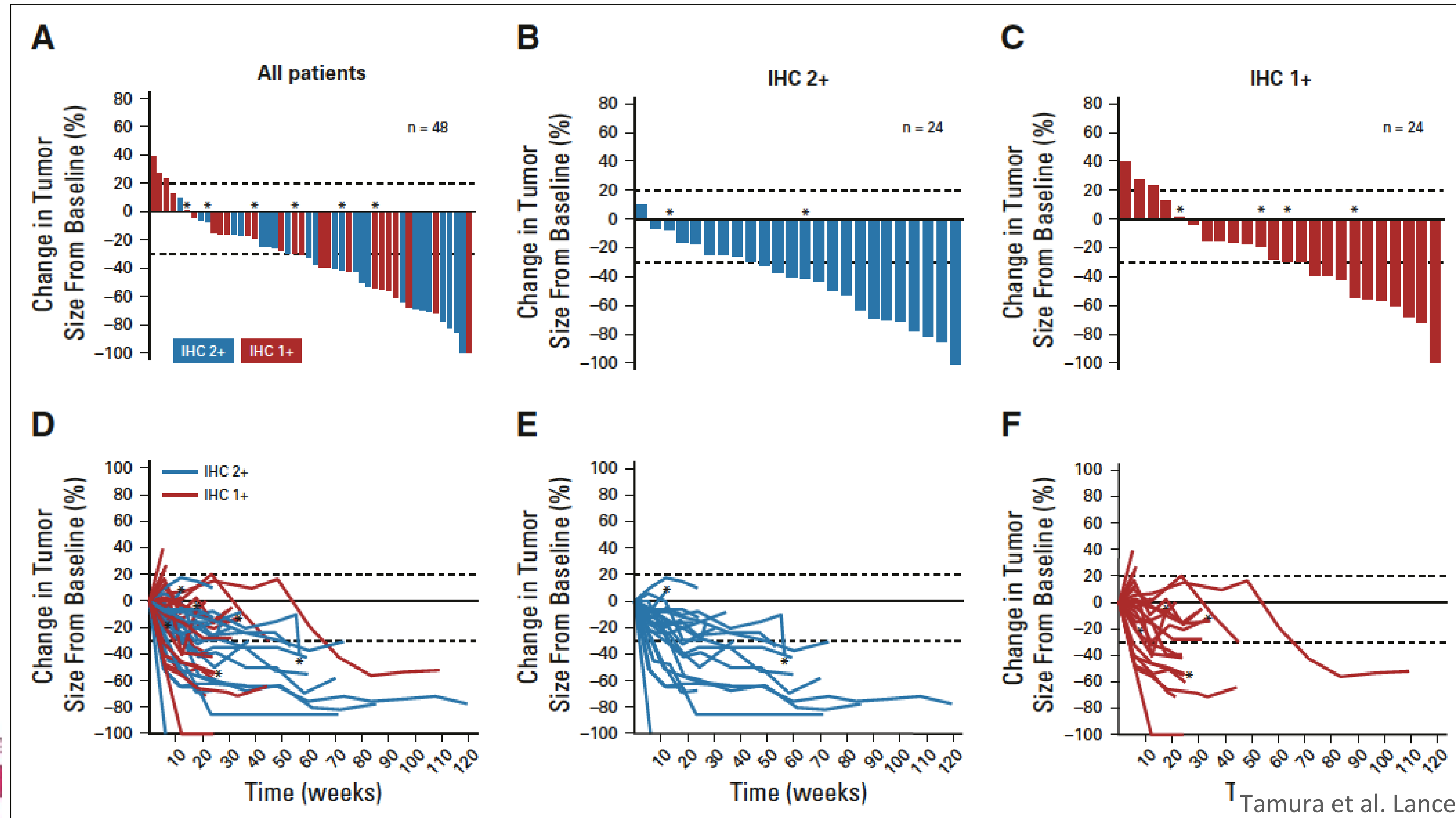
DS-8201a foi efetivo contra modelos HER2+ (KPL4, JIMT-1, e Capan-1)



DS-8201a não foi efetivo no HER2-negativo (GCIY)

Ogitani et al. Clin Cancer Res 2016;22:5097-5108.

Fase I de T-DXd em HER2-low e mutação HER2



Fase I de T-Dxd em HER2-low e mutação HER2

TABLE 1. Patient Demographics and Baseline Characteristics

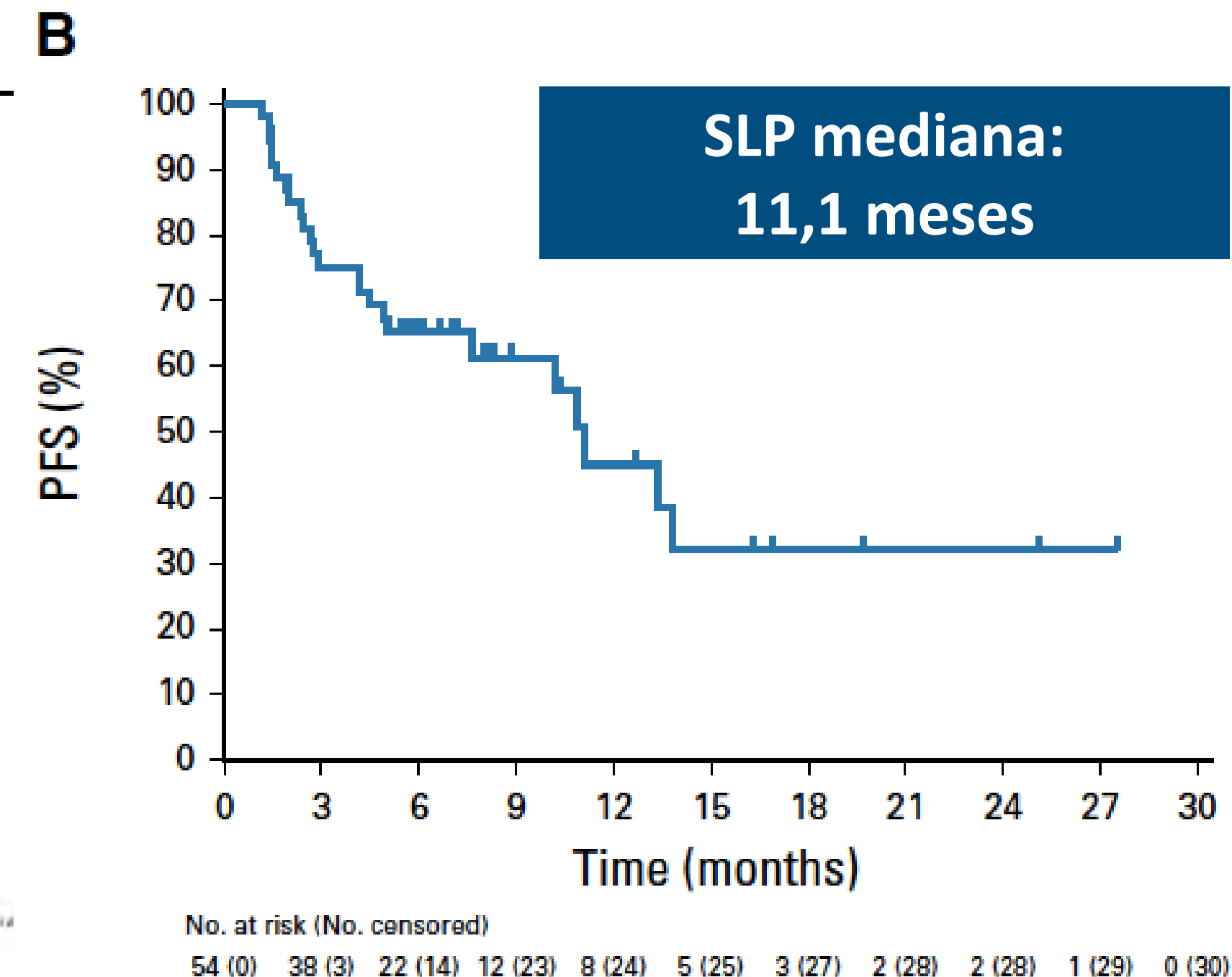
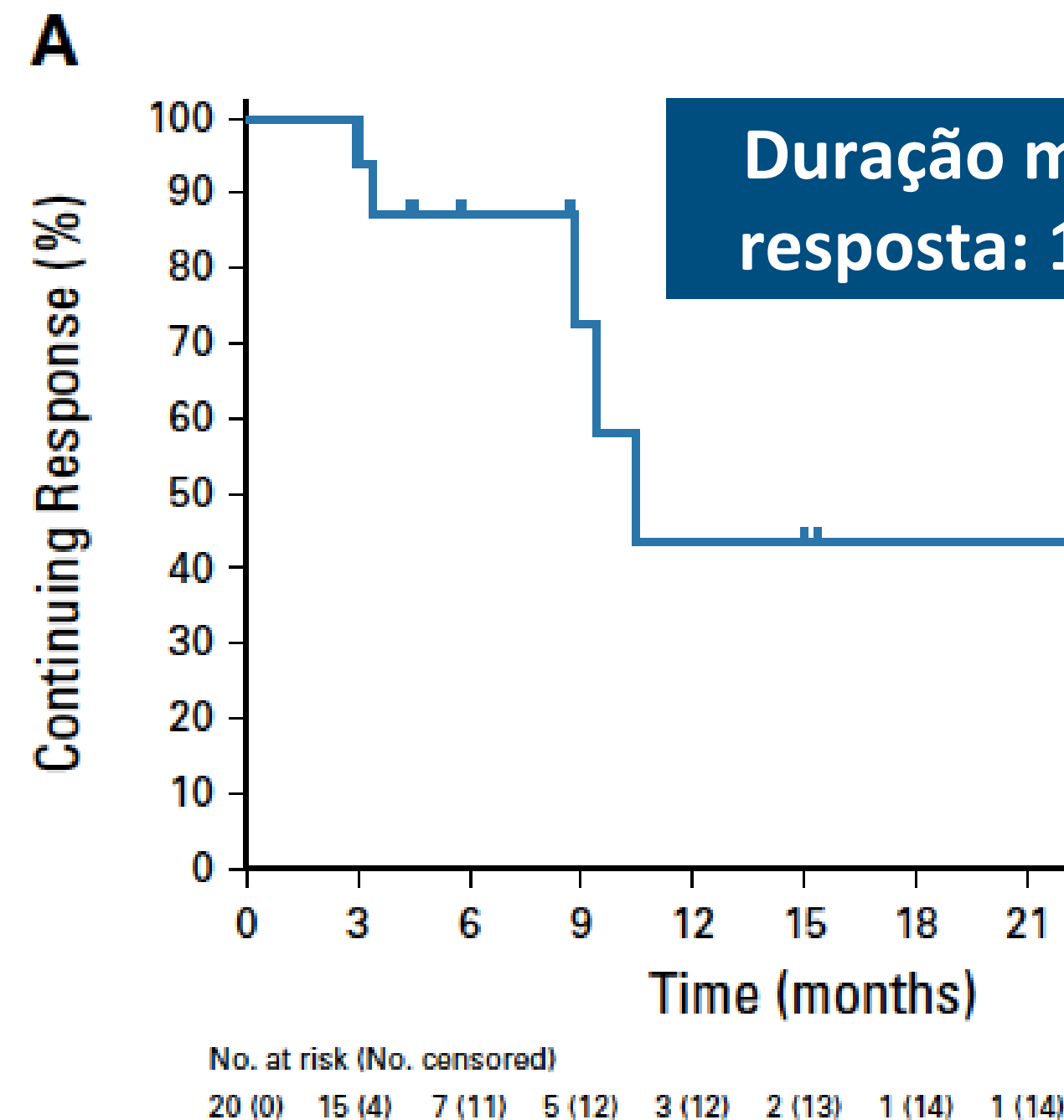
Characteristic	HER2-Low Breast Cancer N = 54
Median age (range), years	56.6 (33-75)
Country	
Japan	27 (50.0)
United States	27 (50.0)
ECOG performance status	
0	36 (66.7)
1	18 (33.3)
Median time from initial diagnosis (range), months ^a	105.0 (13.0-290.3)
Median No. of prior cancer regimens (range)	7.5 (2-16)
≥ 5 prior cancer regimens	45 (83.3)
CDK4/6 inhibitor	16 (29.6)
HER2-targeted therapy	10 (18.5)
Trastuzumab	10 (18.5)
Pertuzumab	7 (13.0)
T-DM1	5 (9.3)
Other	1 (1.9)

Previous cancer surgery	48 (88.9)
HER2 expression (IHC) by local assessment ^b	
2+ (ISH-)	26 (48.1)
1+	28 (51.9)
0	0
Hormone receptor status	
Positive	47 (87.0)
Negative	7 (13.0)
Sites of metastases at study entry	
Bone	34 (63.0)
Liver	29 (53.7)
Lung	14 (25.9)
Brain	5 (9.3)

Fase I de T-DXd em HER2-low e mutação HER2

TABLE 2. Clinical Activity Outcomes for HER2-Low Patients

Outcome	Overall Population	
	Investigator Report N = 54	Central Review N = 54
Median treatment duration (IQR), months	6.1 (3.4-9.0)	
Confirmed best overall response		
CR	0	0
PR	24 (44.4)	20 (37.0)
SD	21 (38.9)	27 (50.0)
PD	9 (16.7)	6 (11.1)
NE	0	1 (1.9)
Confirmed ORR	24 (44.4)	20 (37.0)
95% CI	30.9 to 58.6	24.3 to 51.3
Confirmed DCR ^a	45 (83.3)	47 (87.0)
95% CI	70.7 to 92.1	75.1 to 94.6
DOR, months ^b		
Median (95% CI)	11.0 (4.5 to 12.8)	10.4 (8.8 to NE)
Min, max	2.1+, 26.3+	1.4+, 26.3+
TTR, months ^c		
Median (95% CI)	2.8 (2.6 to 2.9)	2.6 (1.3 to 3.1)
Min, max	1.2, 13.9	1.2, 16.4
PFS, months		
Median (95% CI)	8.0 (5.6 to 13.9)	11.1 (7.6 to NE)
Min, max	0.7, 27.5+	1.2, 27.5+



Atividade promissora em HER2 low

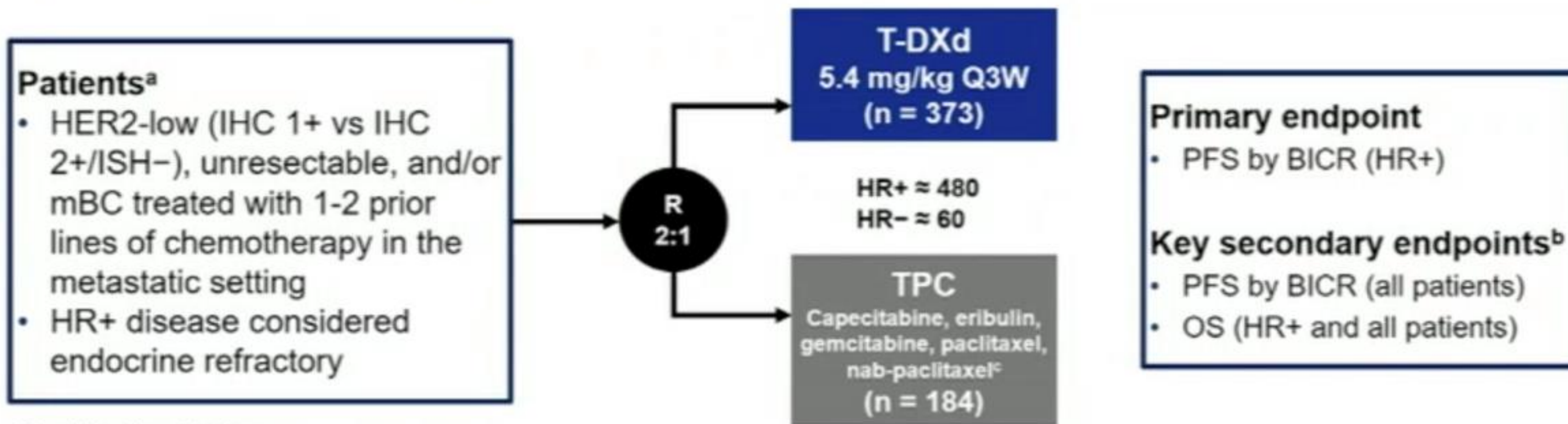
HER2-low é preditivo de resposta a ADC anti-HER2

Os estudos DESTINY-breast (DB) estão mudando a forma de tratar CA mama e definindo um novo subgrupo de pacientes

Destiny Breast-04

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

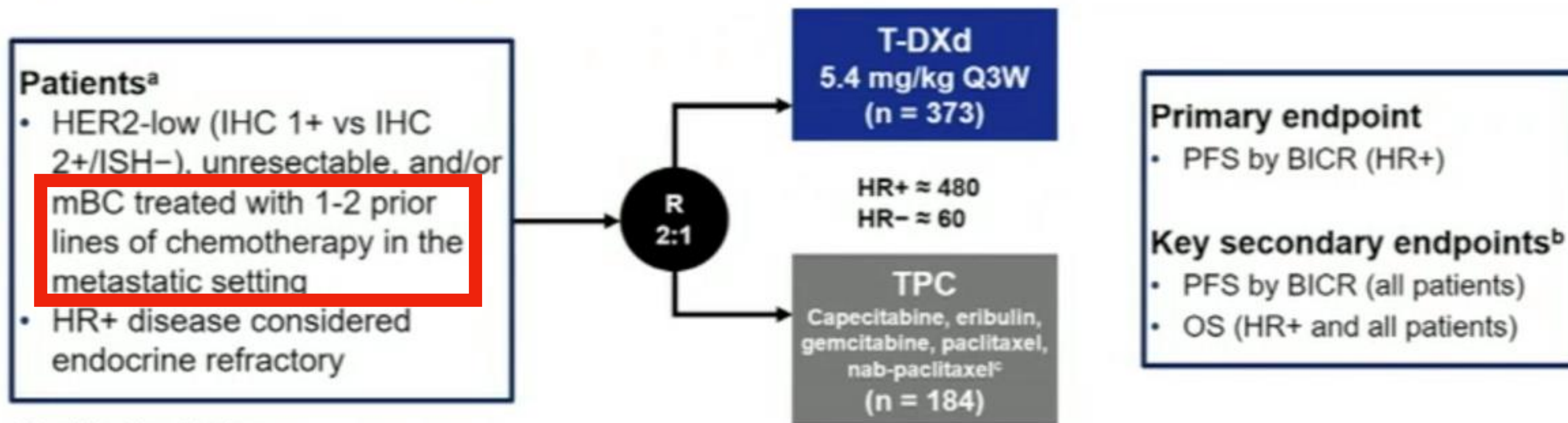


Stratification factors

- Centrally assessed HER2 status^d (IHC 1+ vs IHC 2+/ISH-)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR-

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

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Stratification factors

- Centrally assessed HER2 status^d (IHC 1+ vs IHC 2+/ISH-)
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Prior Therapies

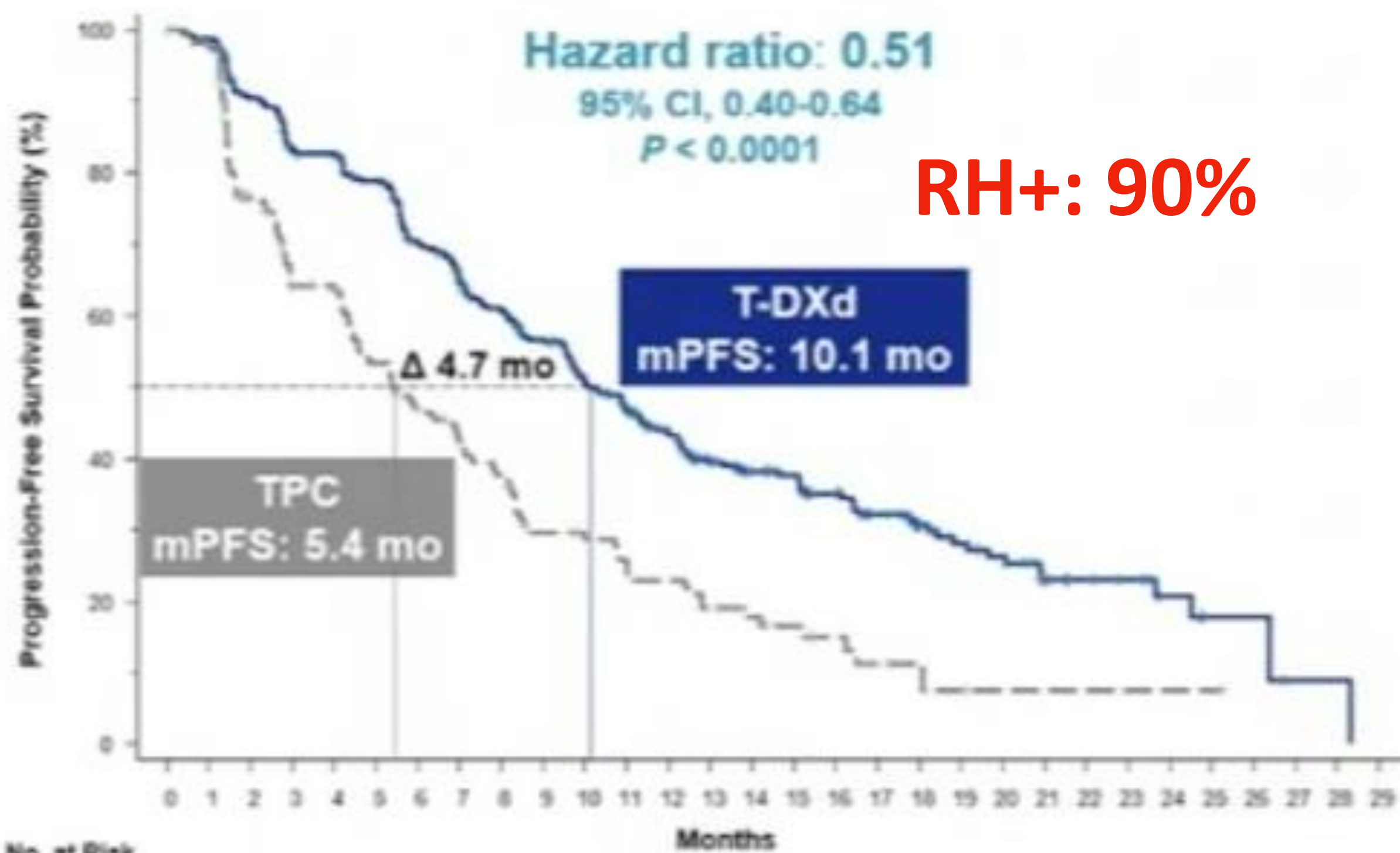
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

>1L

Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

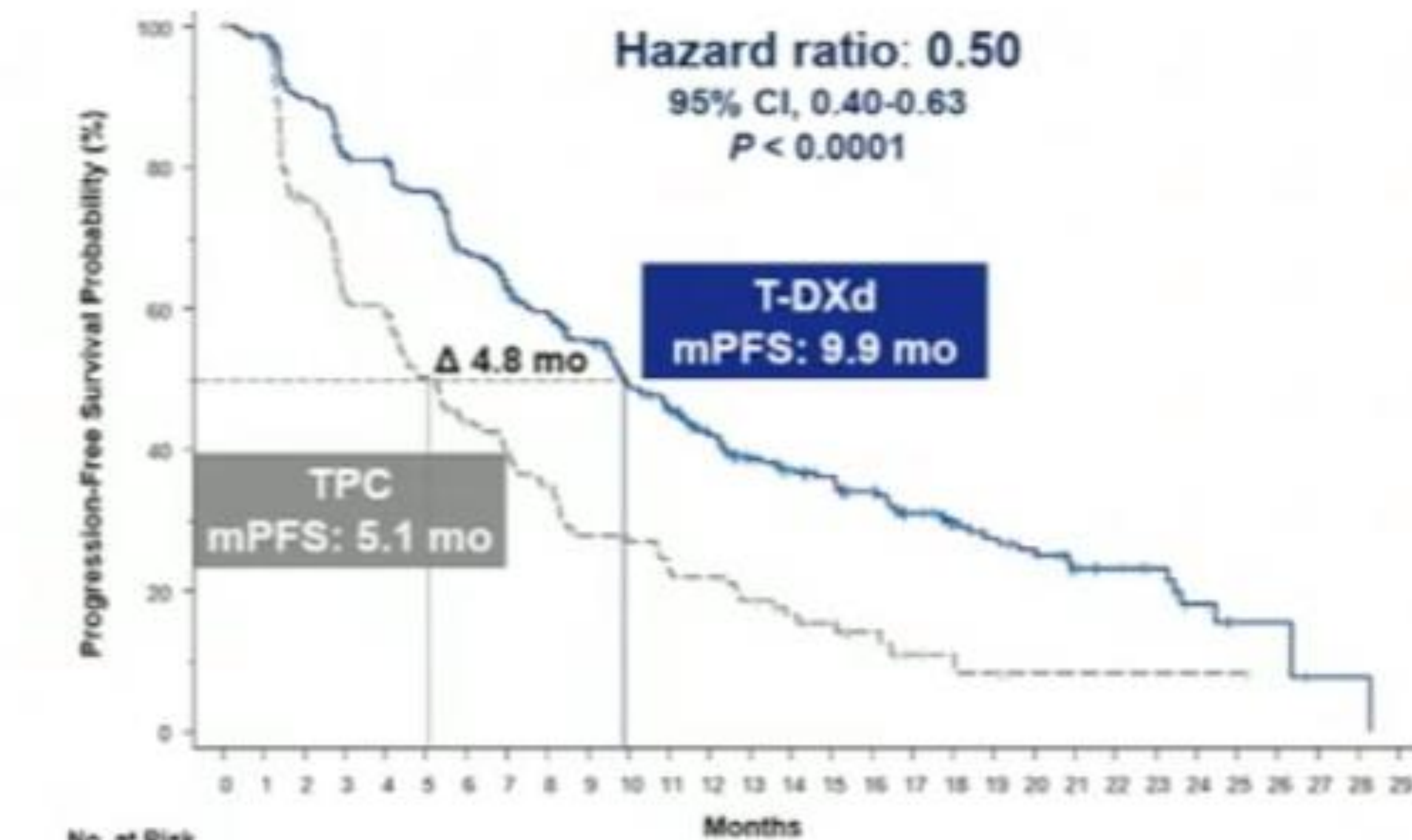
PFS in HR+ and All Patients

Hormone receptor-positive



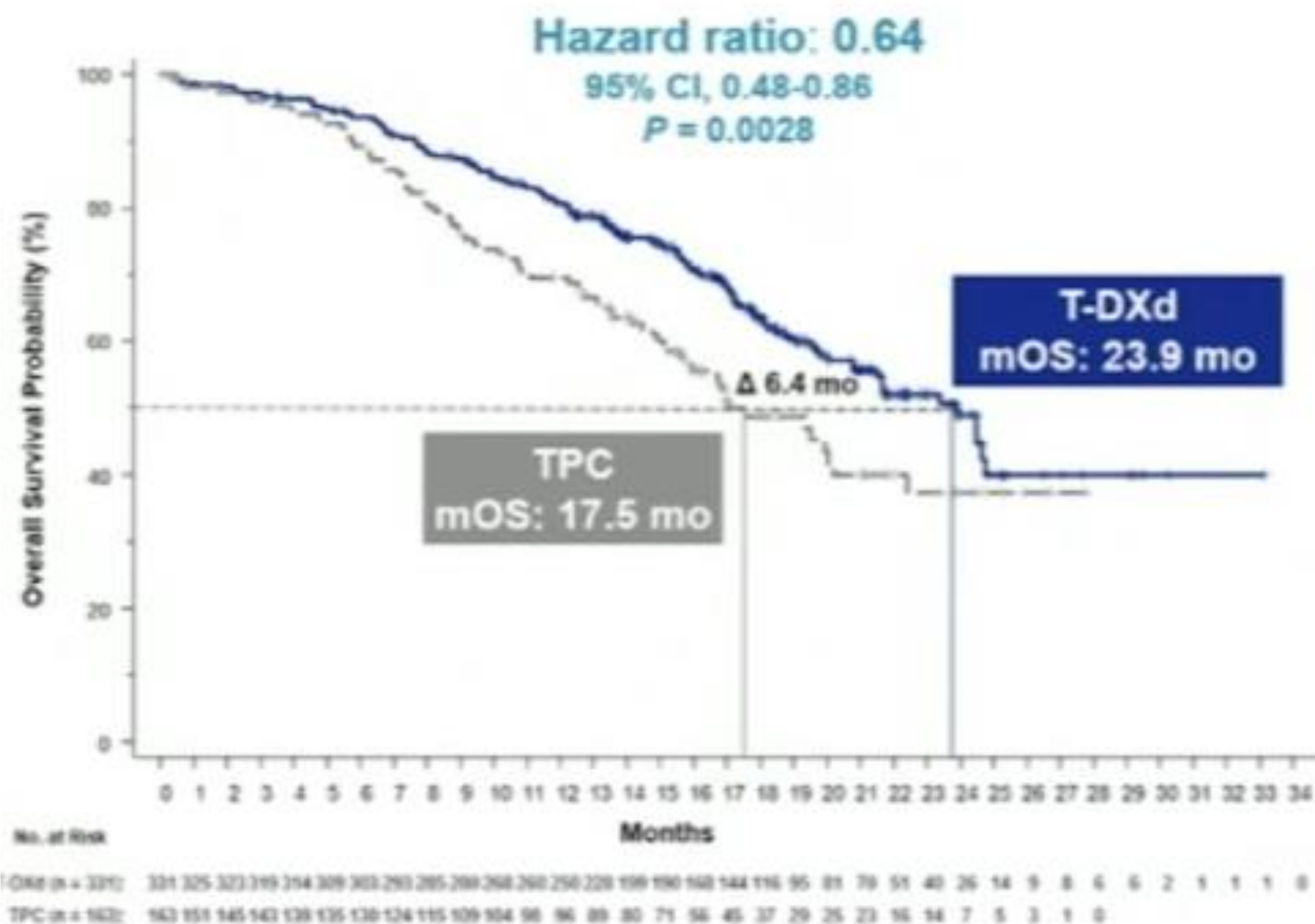
RH+: 90%

All patients

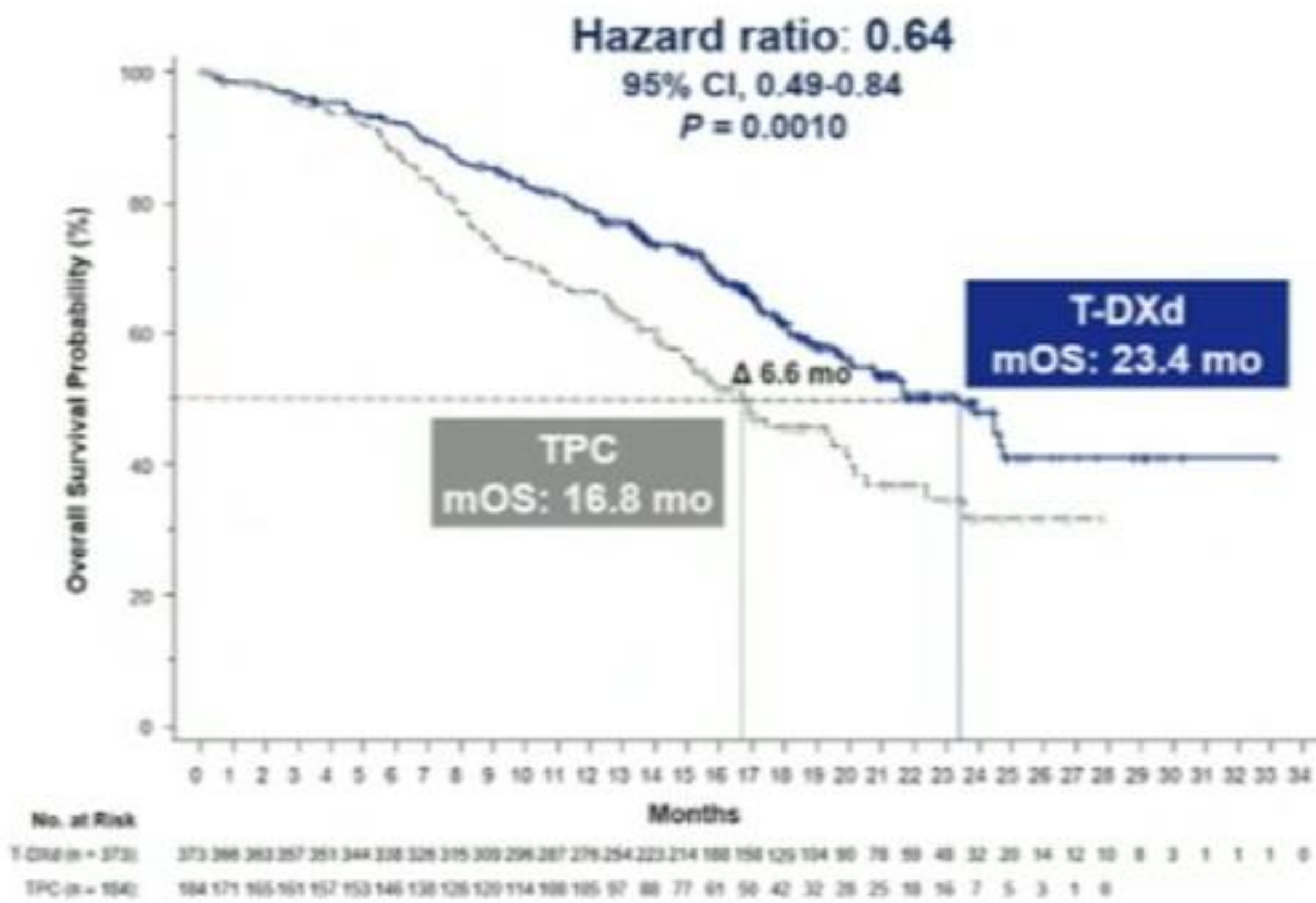


OS in HR+ and All Patients

Hormone receptor-positive

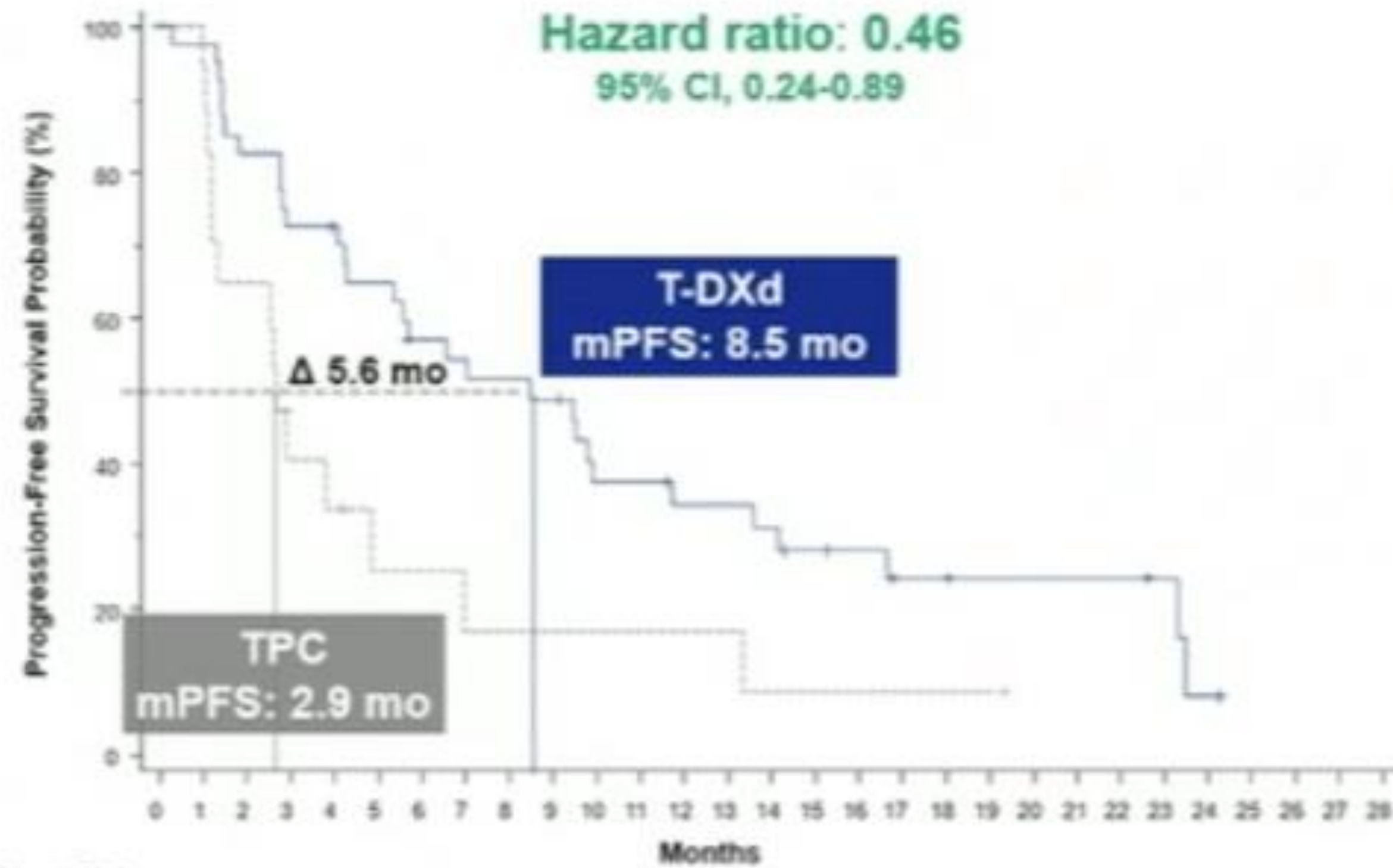


All patients



PFS and OS in HR- (Exploratory Endpoints)

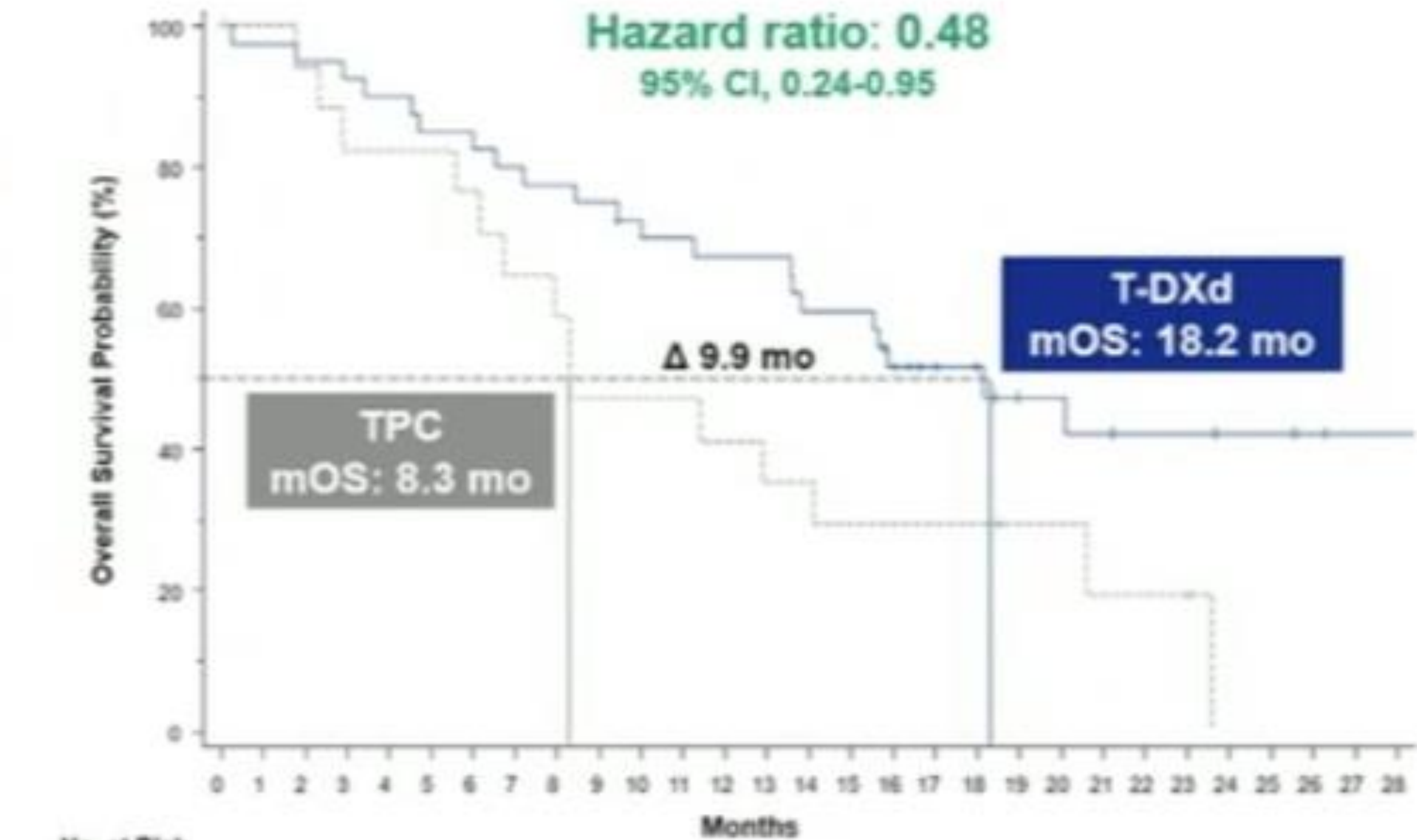
PFS



No. at Risk

DXd (n=40)	40	39	33	29	26	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0
TPC (n=18)	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	1	0	0	0	0	0

OS

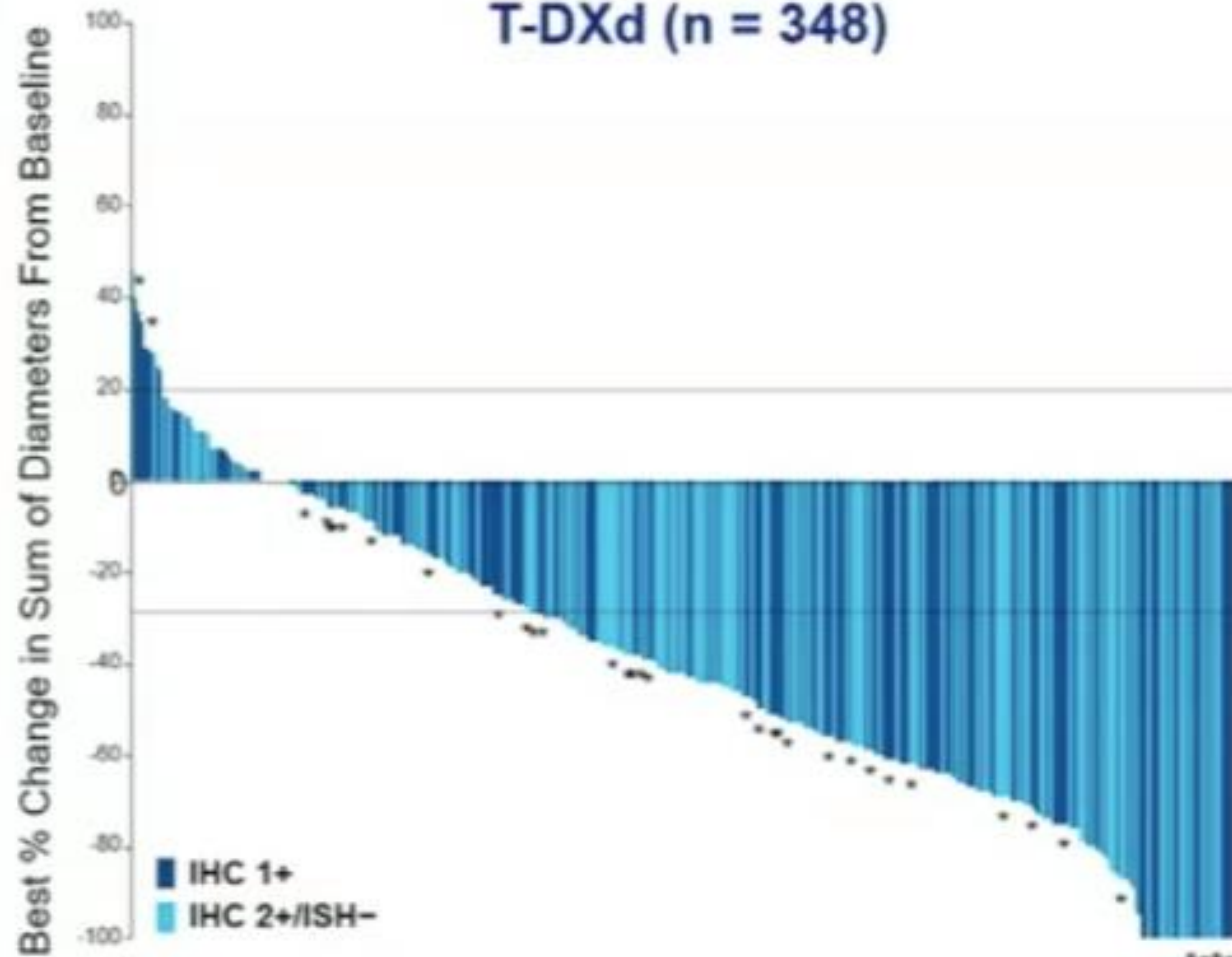


No. at Risk

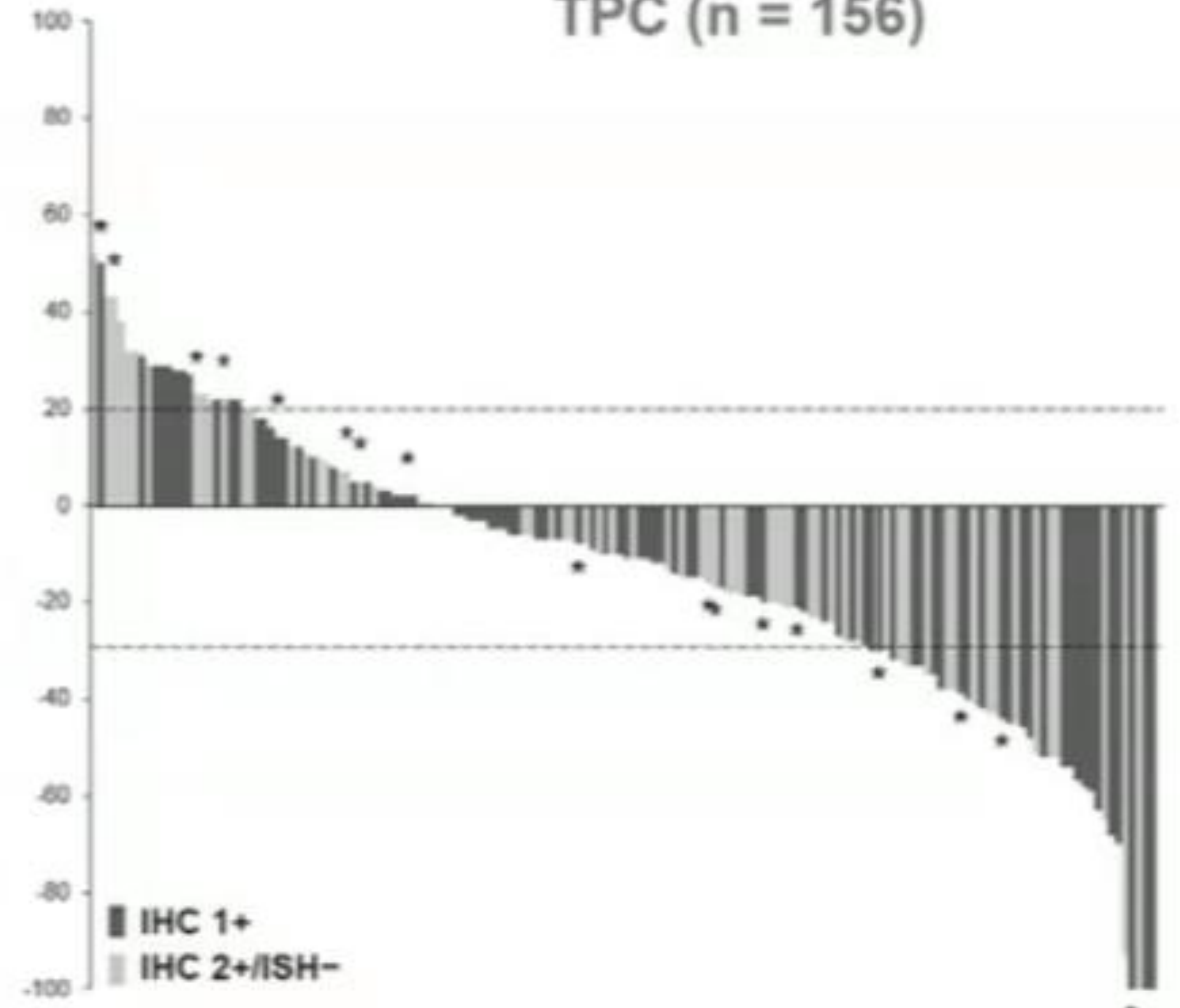
T-DXd (n=40)	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n=18)	18	17	16	14	14	14	3	11	10	8	8	7	6	6	5	5	5	5	5	3	3	2	2	2	0	0	0	0	0

Best Change in Target Lesions (All Patients)

T-DXd (n = 348)



TPC (n = 156)



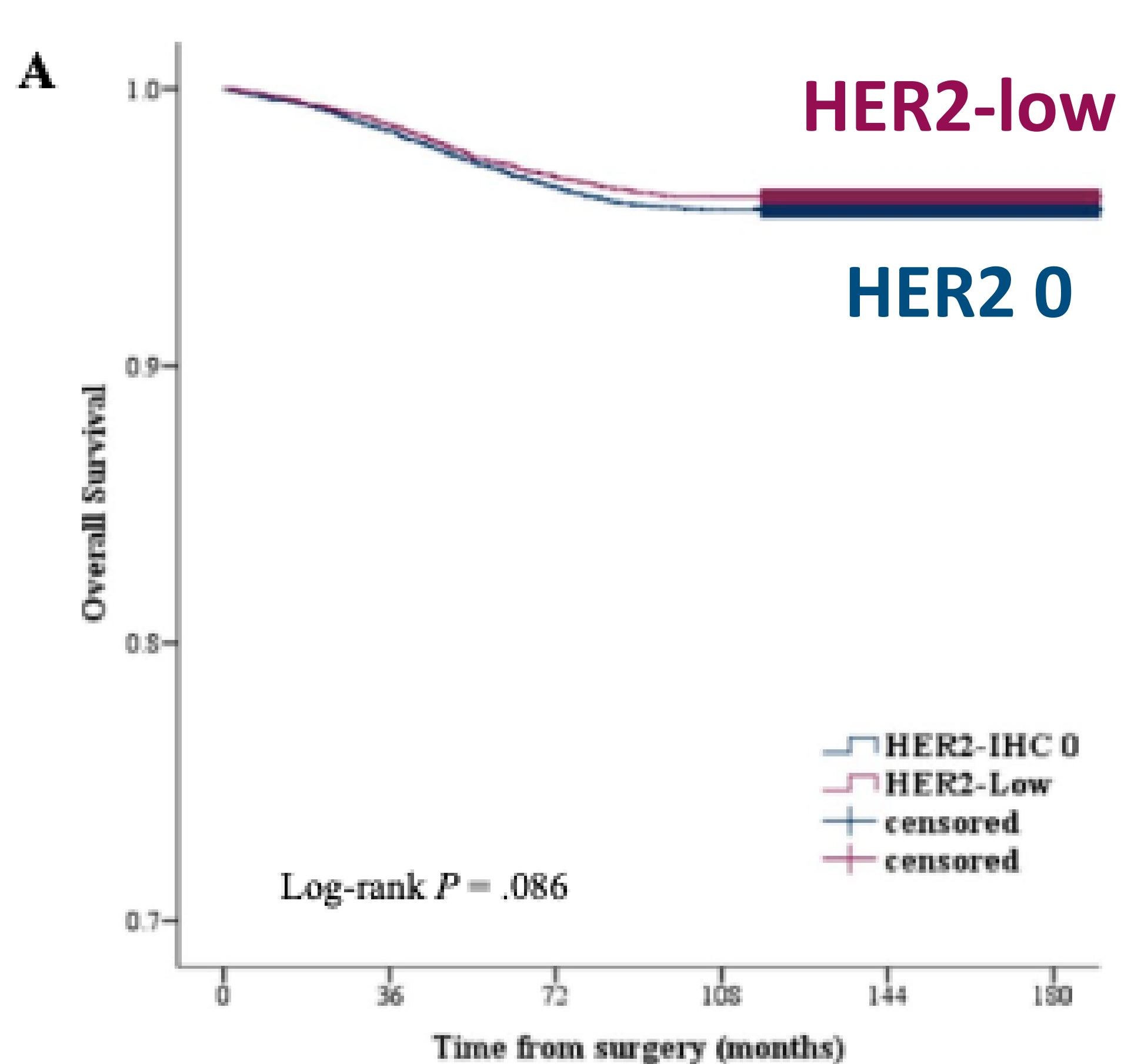
*Patients with HR- disease

Destiny Breast-04



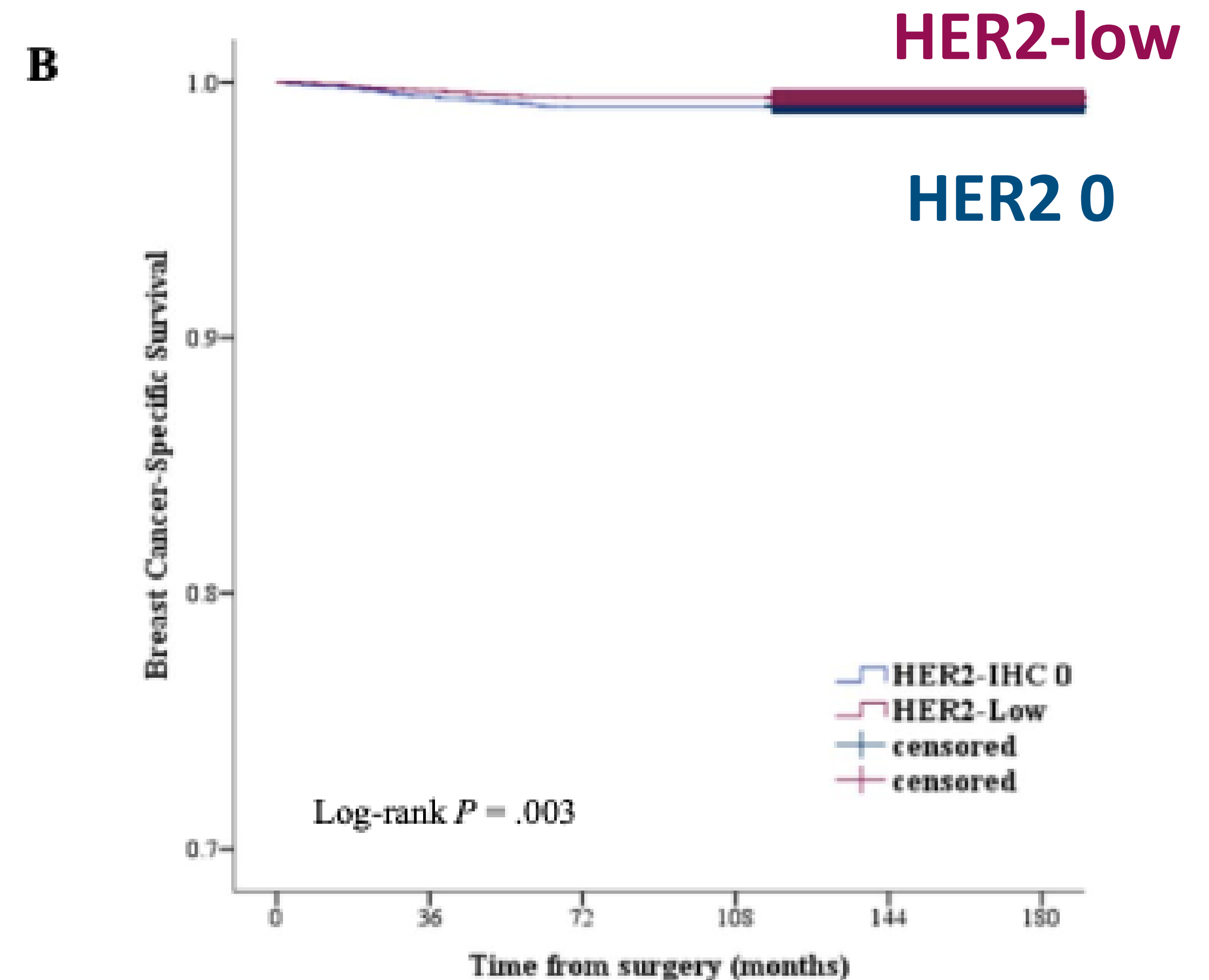
HER2-low é prognóstico?

Sem diferença entre HER2-low e HER2 0 no RH+



No. at risk

HER2-IHC 0	15629	15392	15074	14946	9385	1660
HER2-Low	7910	7807	7657	7602	3696	643

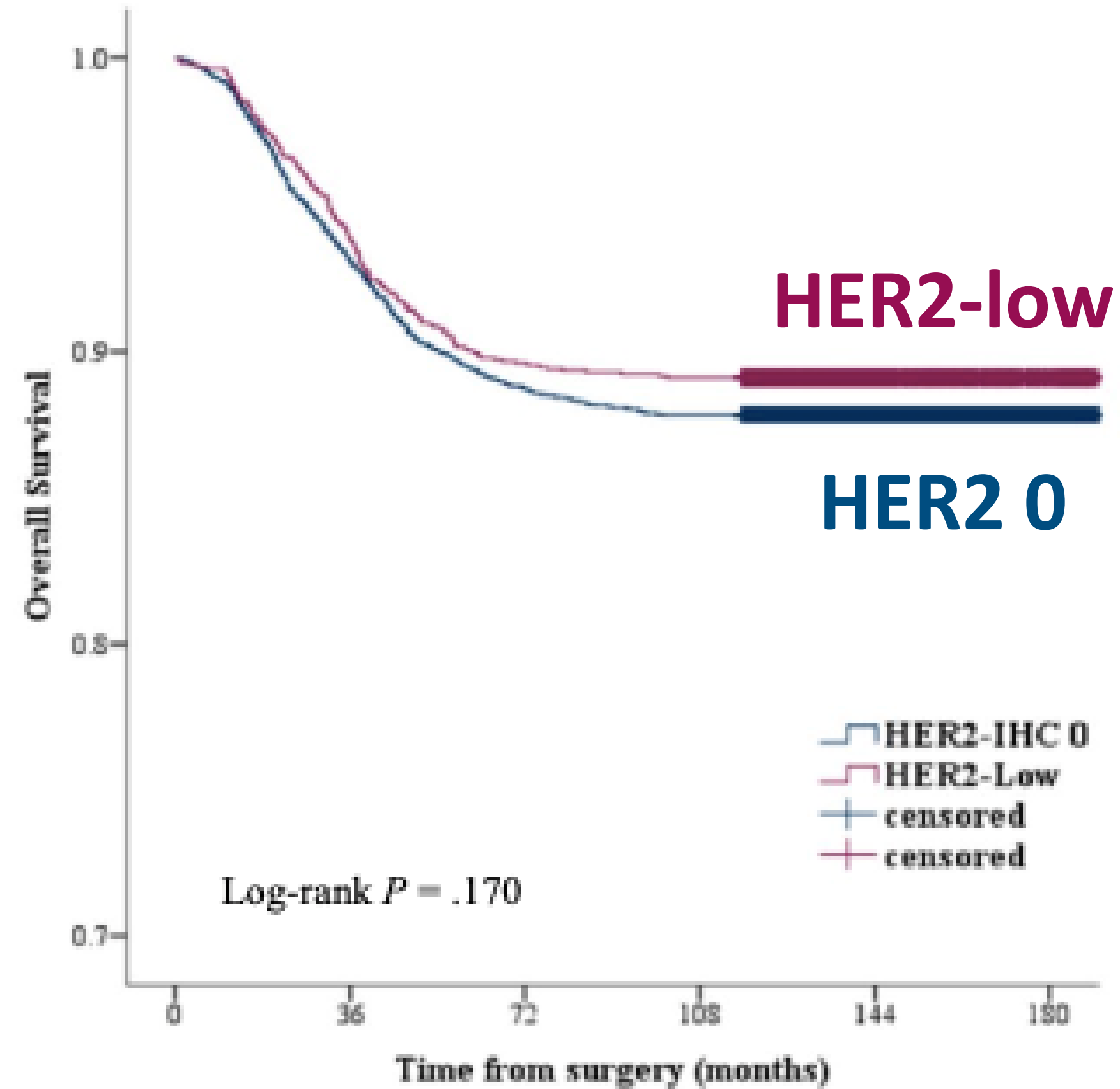


No. at risk

HER2-IHC 0	15629	15543	15477	15477	9800	1772
HER2-Low	7910	7881	7861	7861	3879	679

Sem diferença entre HER2-low e HER2 0 no RH-neg

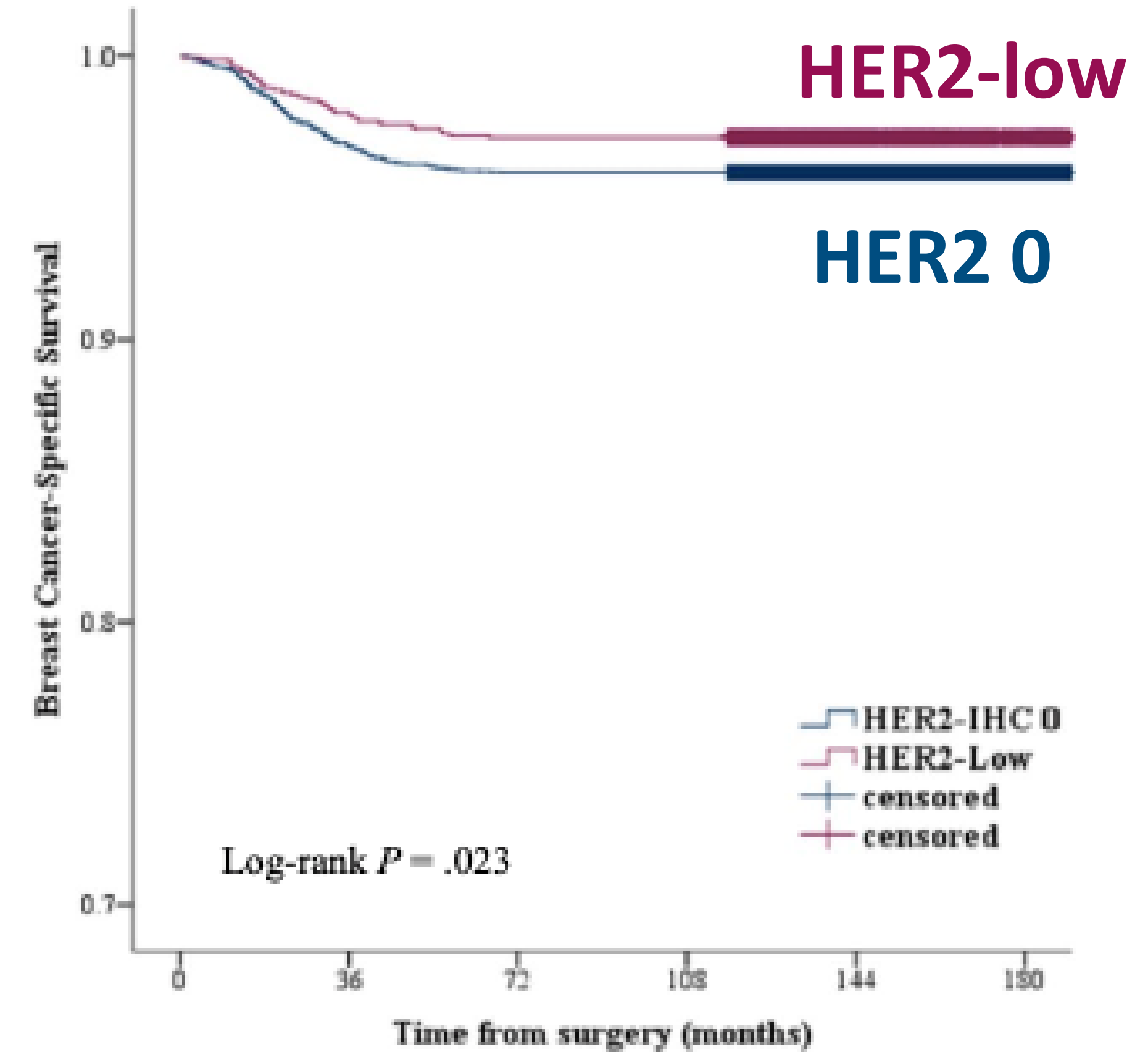
C



No. at risk

HER2-IHC 0	5340	4969	4738	4689	3017	545
HER2-Low	1594	1496	1428	1420	770	173

D



No. at risk

HER2-IHC 0	5340	5170	5118	5118	3284	595
HER2-Low	1594	1561	1547	1547	846	188

Desafios

Sequenciamento de tratamento

Sequenciamento do tto sistêmico EC IV HER2-low

RH+

1L:

- **iCDK4/6 + HT (ML2, ML7, MN3)**

Sequenciamento do tto sistêmico EC IV HER2-low

RH+

1L:

- iCDK4/6 + HT (ML2, ML7, MN3)

2L:

- iCDK4/6 + HT (ML3, MN2)
- mutPIK3CA: fulv + alp (SOLAR-1)
- mBRCA1/2: olaparibe (OlympiAD)

Sequenciamento do tto sistêmico EC IV HER2-low

RH+

1L:

- iCDK4/6 + HT (ML2, ML7, MN3)

2L:

- iCDK4/6 + HT (ML3, MN2)
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3L: esgotar HT ou fazer QT para depois usar T-Dxd?

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RH+

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Sacituzumabe-govitecan (TROPiCS-02)**

Sequenciamento do tto sistêmico EC IV HER2-low

RH+

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**3L: esgotar HT ou fazer QT para depois usar T-Dxd?
Sacituzumabe-govitecan (TROPiCS-02)**

Foto x Filme!!!



Créditos da idéia: Dra. Solange Sanches

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^a

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	Subtype/Biomarker	Regimen
First Line	No germline <i>BRCA1/2</i> mutation ^b	Systemic chemotherapy see BINV-Q (5)
	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) ^c (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative ^d	Fam-trastuzumab deruxtecan-nxki ^e (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan ^f (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

Sequenciamento do tto sistêmico EC IV HER2-low

RH-neg

1L:

- PDL1 CPS \geq 10: pembro + QT
- PDL1 CPS $<$ 10: QT

Sequenciamento do tto sistêmico EC IV HER2-low

RH-neg

1L:

- PDL1 CPS \geq 10: pembro + QT
- PDL1 CPS $<$ 10: QT

2L:

- mBRCA1/2: olaparibe (OlympiAD)
- T-Dxd (DB-04)

Sequenciamento do tto sistêmico EC IV HER2-low

RH-neg

1L:

- PDL1 CPS \geq 10: pembro + QT
- PDL1 CPS $<$ 10: QT

2L:

- mBRCA1/2: olaparibe (OlympiAD)
- T-Dxd (DB-04)

3L: sacituzumabe-govitecan (ASCENT) - após T-Dxd?

Sequenciamento do tto sistêmico EC IV HER2-low

RH-neg

1L:

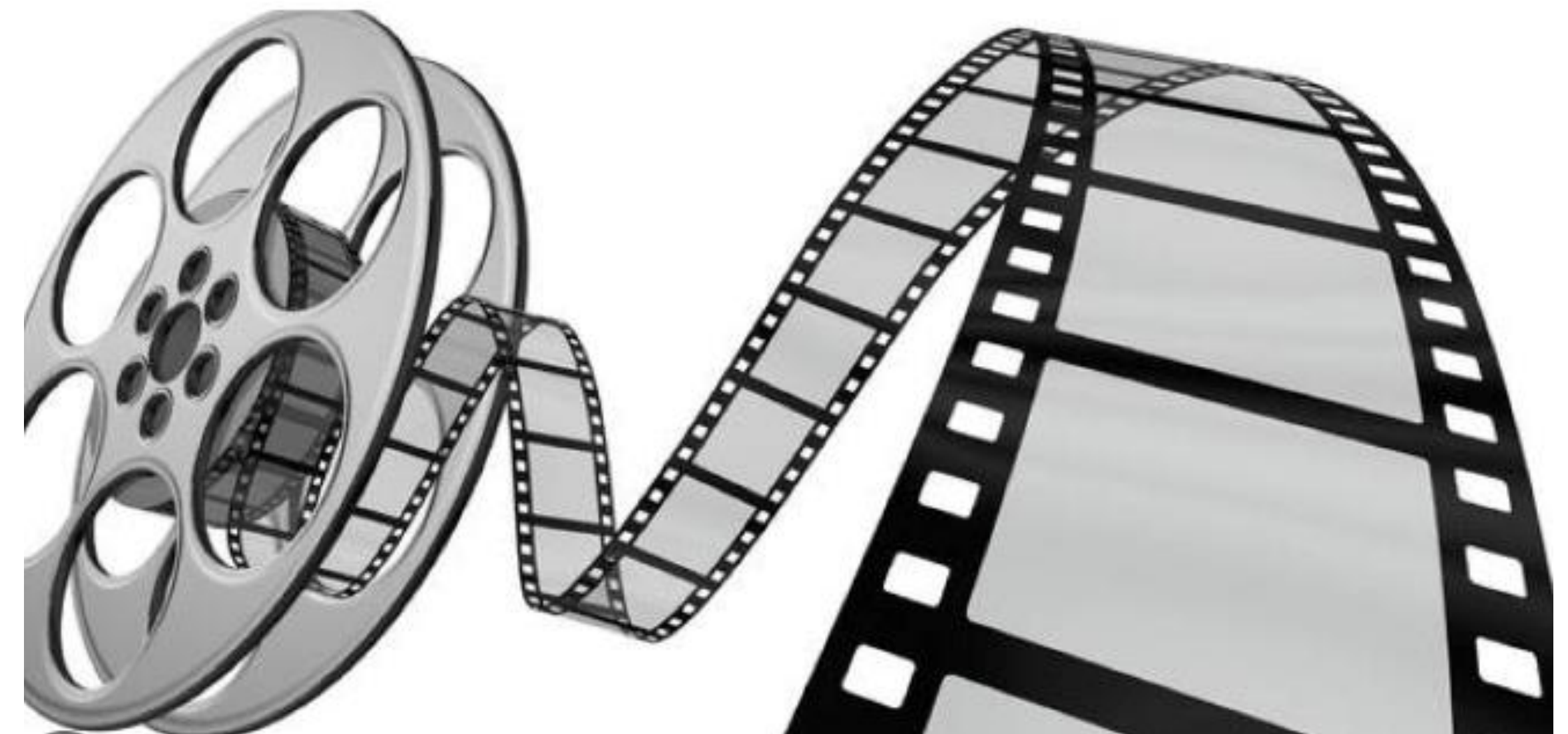
- PDL1 CPS \geq 10: pembro + QT
- PDL1 CPS $<$ 10: QT

2L:

- mBRCA1/2: olaparibe (OlympiAD)
- T-Dxd (DB-04)

3L: sacituzumabe-govitecan (ASCENT) - após T-Dxd?

Foto x Filme!!!



Créditos da idéia: Dra. Solange Sanches

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^a

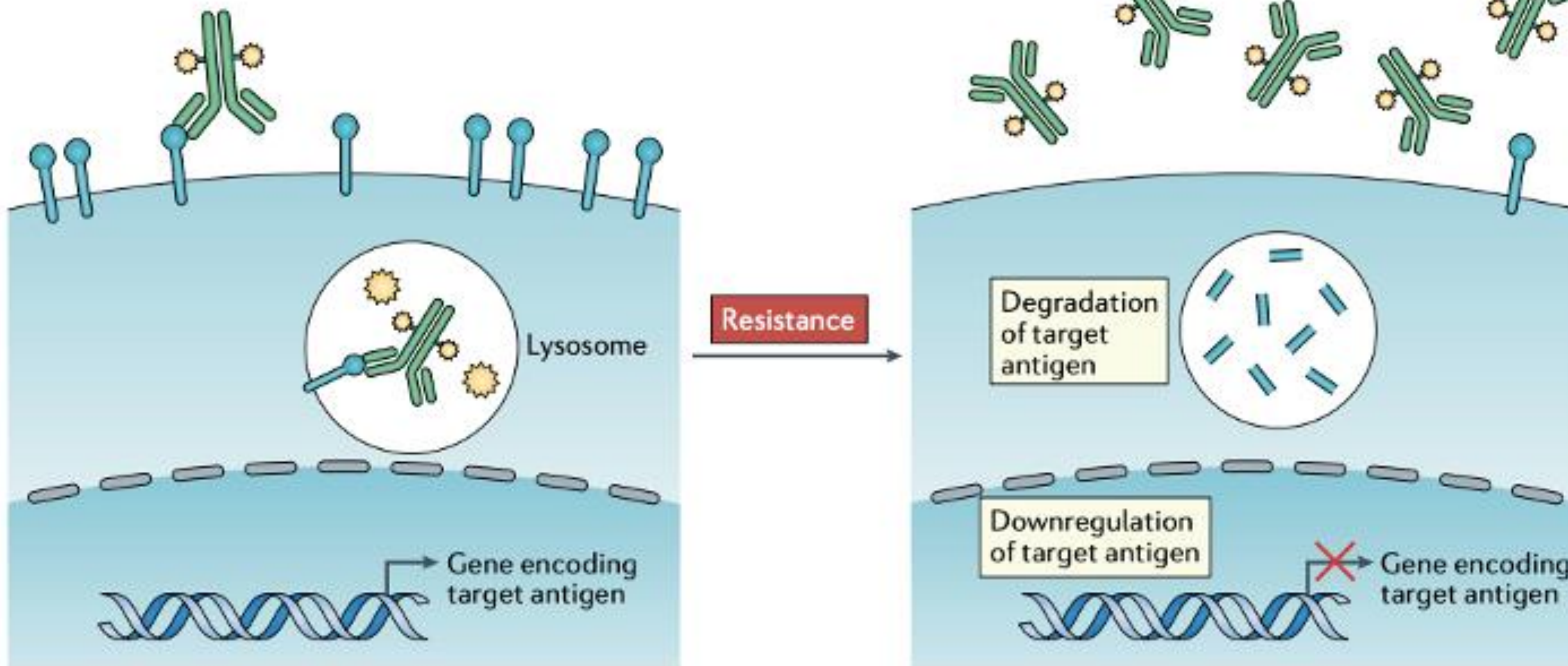
HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	Subtype/Biomarker	Regimen
First Line	PD-L1 CPS $\geq 10^9$ regardless of germline <i>BRCA</i> mutation status ^b	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin) ^h (Category 1, preferred)
	PD-L1 CPS $< 10^9$ and no germline <i>BRCA1/2</i> mutation ^b	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS $< 10^9$ and germline <i>BRCA1/2</i> mutation ^b	<ul style="list-style-type: none"> • PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan ⁱ (Category 1, preferred)
	No germline <i>BRCA1/2</i> mutation ^b and HER2 IHC 1+ or 2+/ISH negative ^d	Fam-trastuzumab deruxtecan -nxki ^e (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

Resistência aos ADCs

Resistência aos ADCs

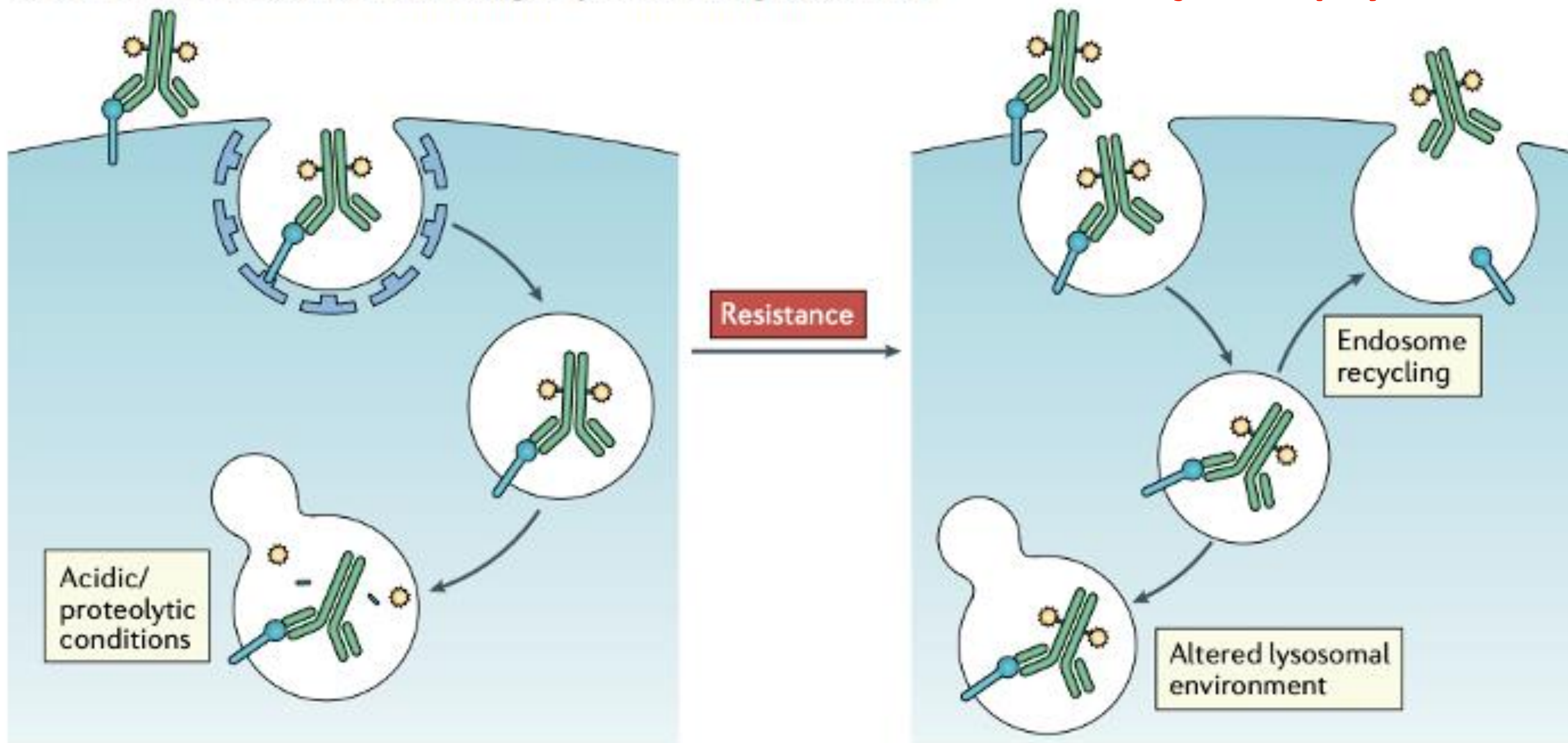
Redução da ligação do ADC

a Antigen downregulation or loss



Resistência aos ADCs

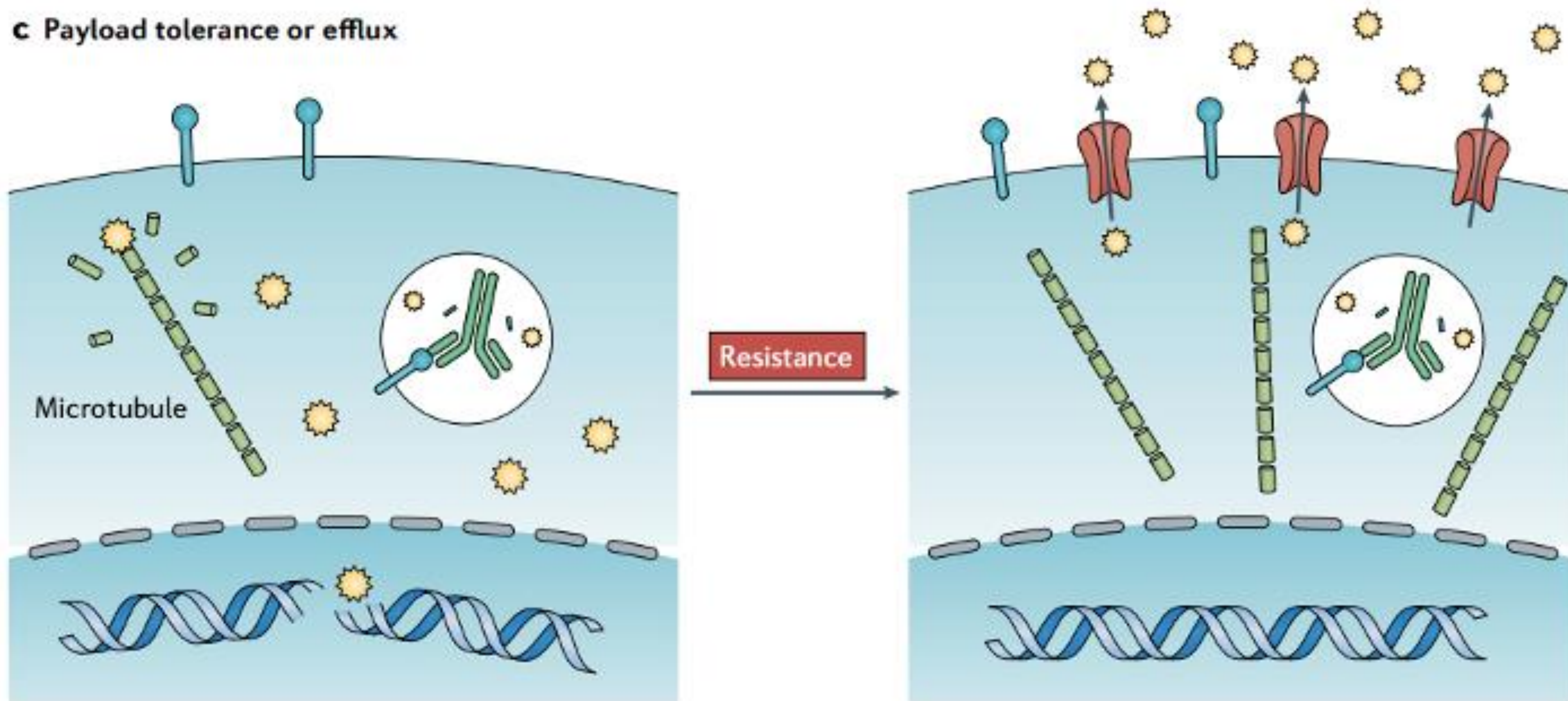
b Alteration of intracellular trafficking or lysosomal drug breakdown



Resistência aos ADCs

Ejeção de partículas do payload que entram no citoplasma

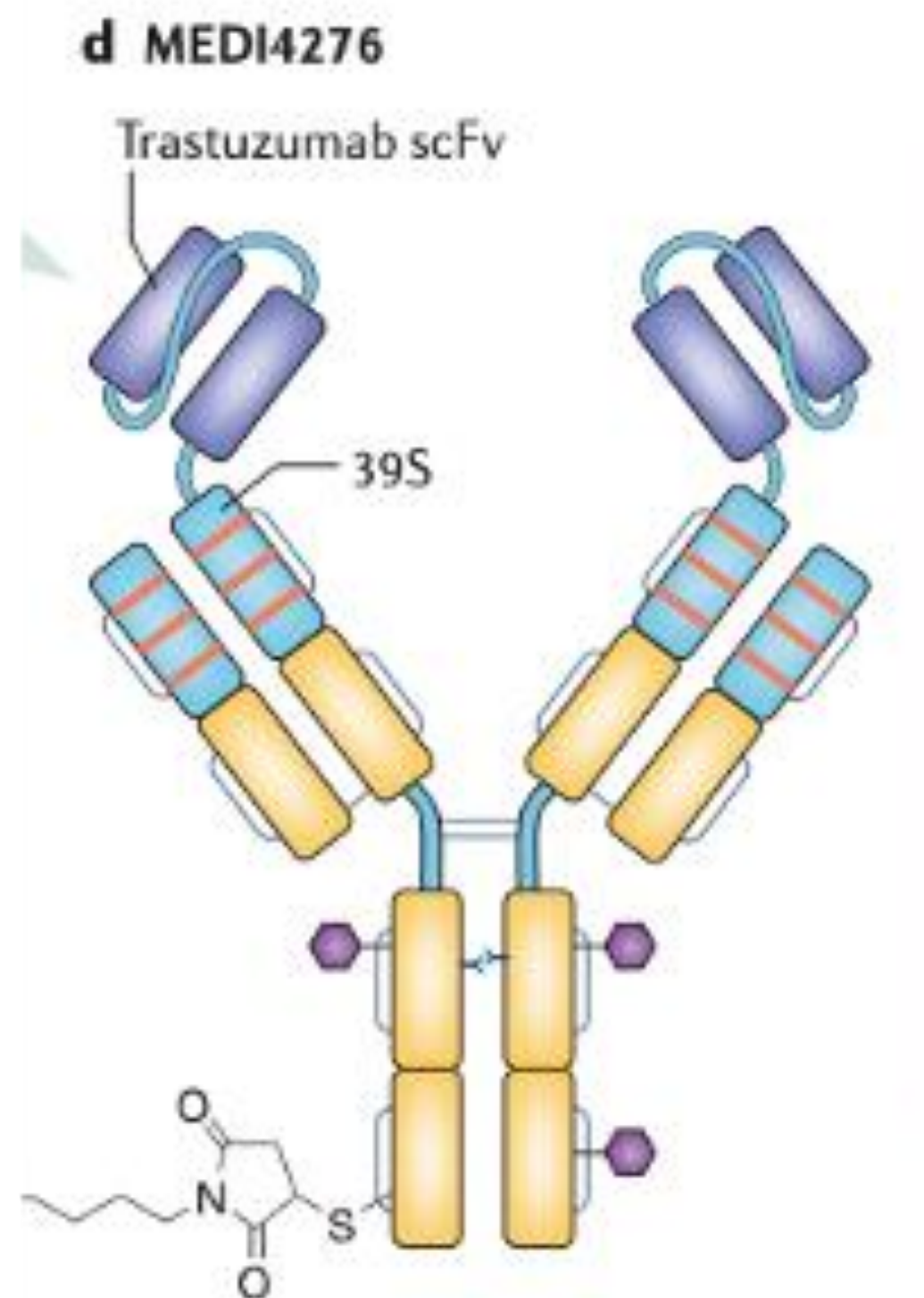
c Payload tolerance or efflux



Como potencializar os ADCs

Ac biespecíficos: ligam-se a 2 antígenos ao mesmo tempo

Ac biparatropicos: 2 epitopos do mesmo antígeno



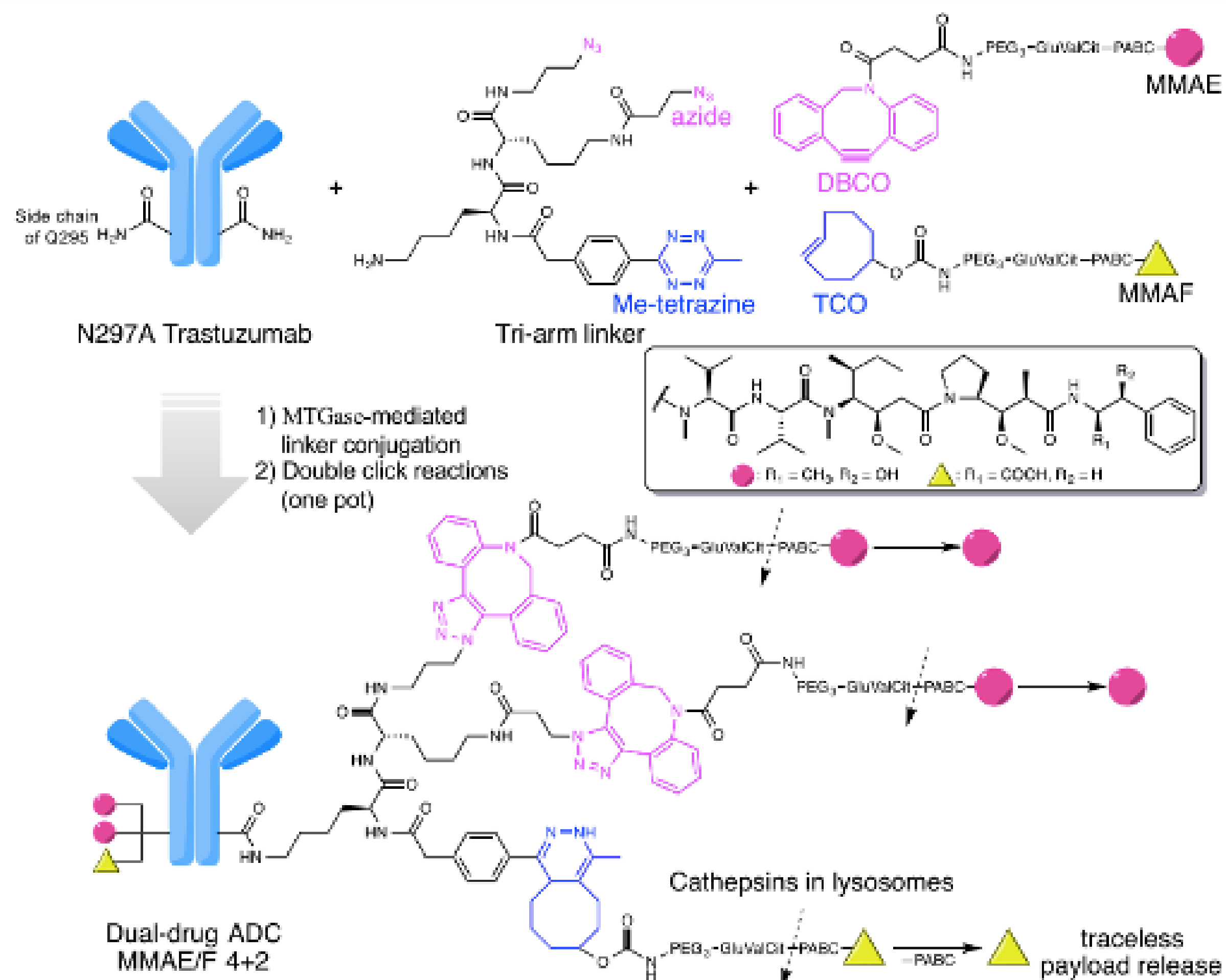
Third generation

- Biparatopic antibody
- Non-cleavable maleimidocaproyl linker attached to engineered heavy-chain cysteine (S239C and S442C)
- 4 tubulysin moieties per IgG
- Additional L234F mutation to abrogate Fc binding

Beck et al. Nat Ver 2017;16:315.

Como potencializar os ADCs

2 payloads



Conclusões

Conclusões

HER2-low é um novo subgrupo que surgiu a partir da resposta ao ADC

Ainda precisamos entender valor prognóstico do HER2-low

Trastuzumabe-deruxtecan muda a perspectiva de tratamento com resultado

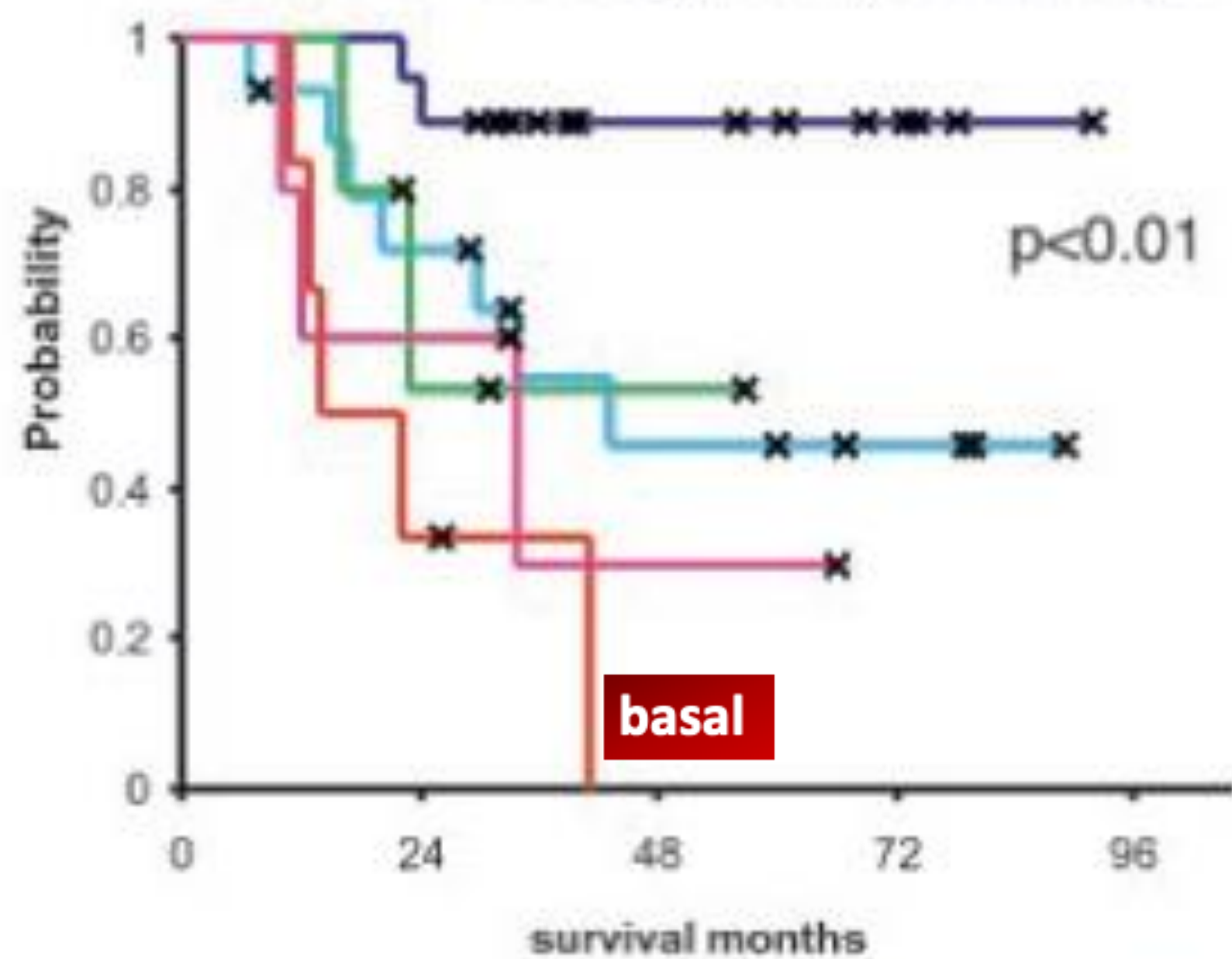
Desafio maior: sequenciamento do tratamento

Melhor entendimento de resistência aos ADCs

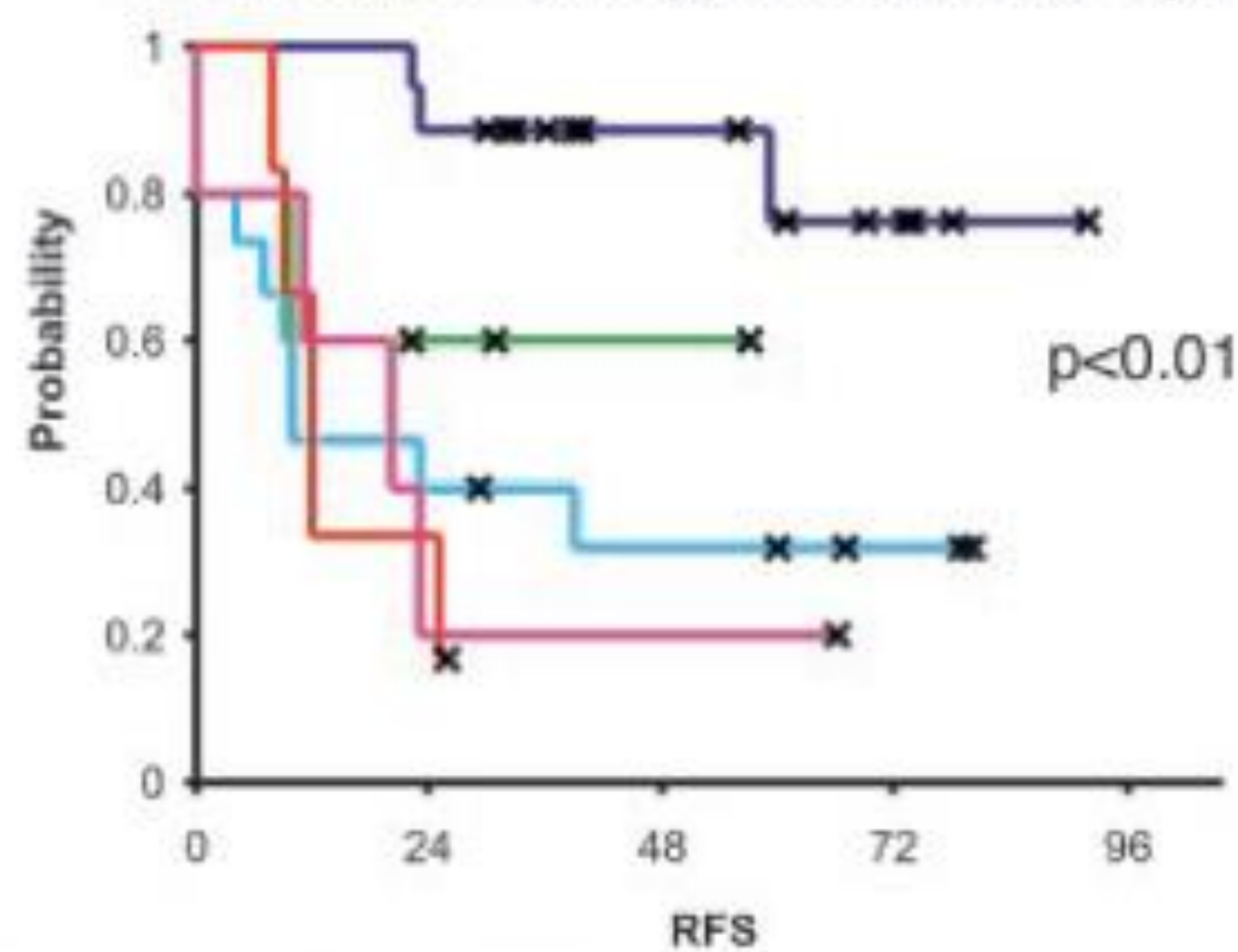
Futuro

Melhorar prognóstico dos TN?

A 5 tumor subtypes (based upon Fig 1)



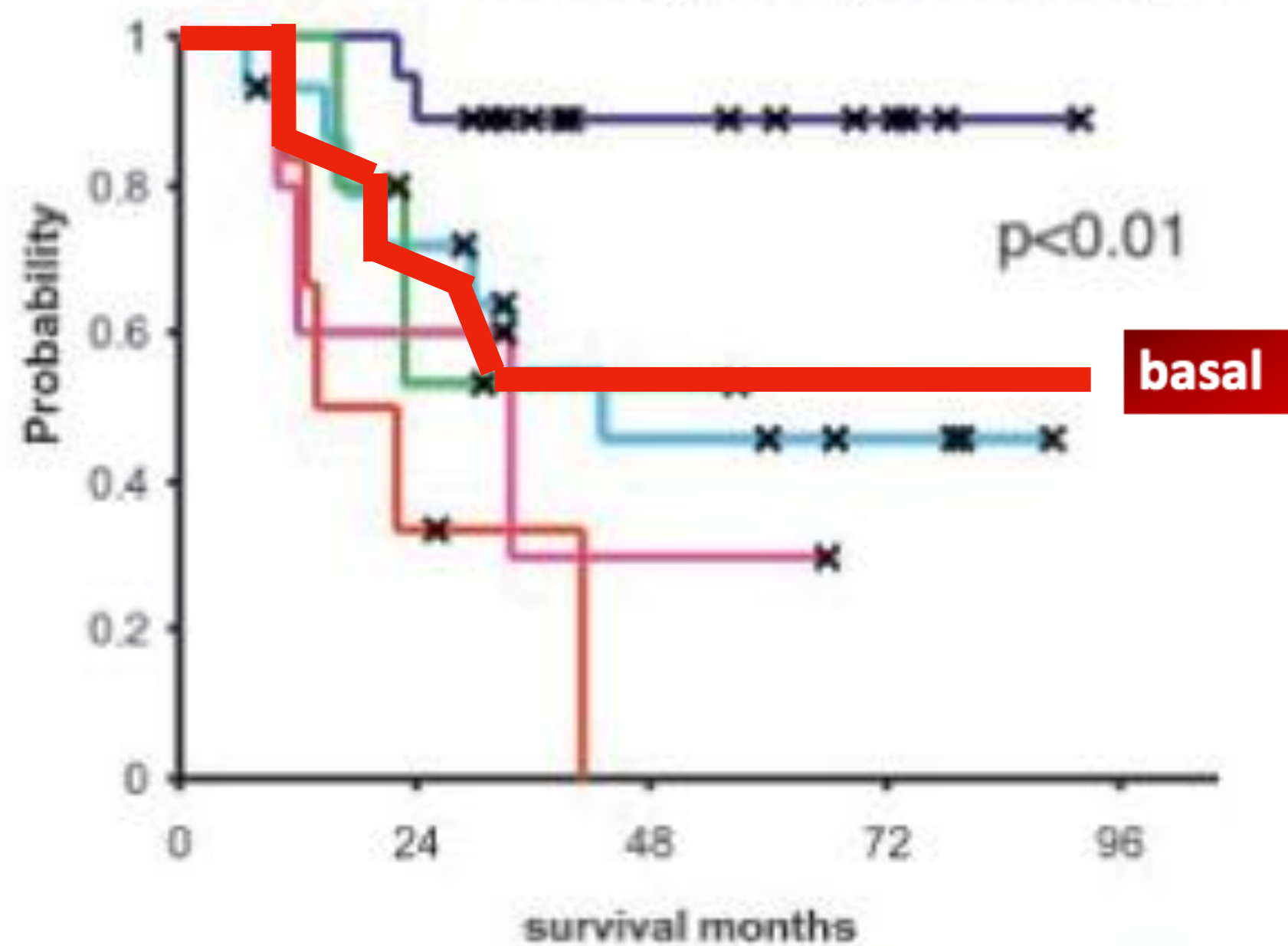
B 5 tumor subtypes (based upon Fig 1)



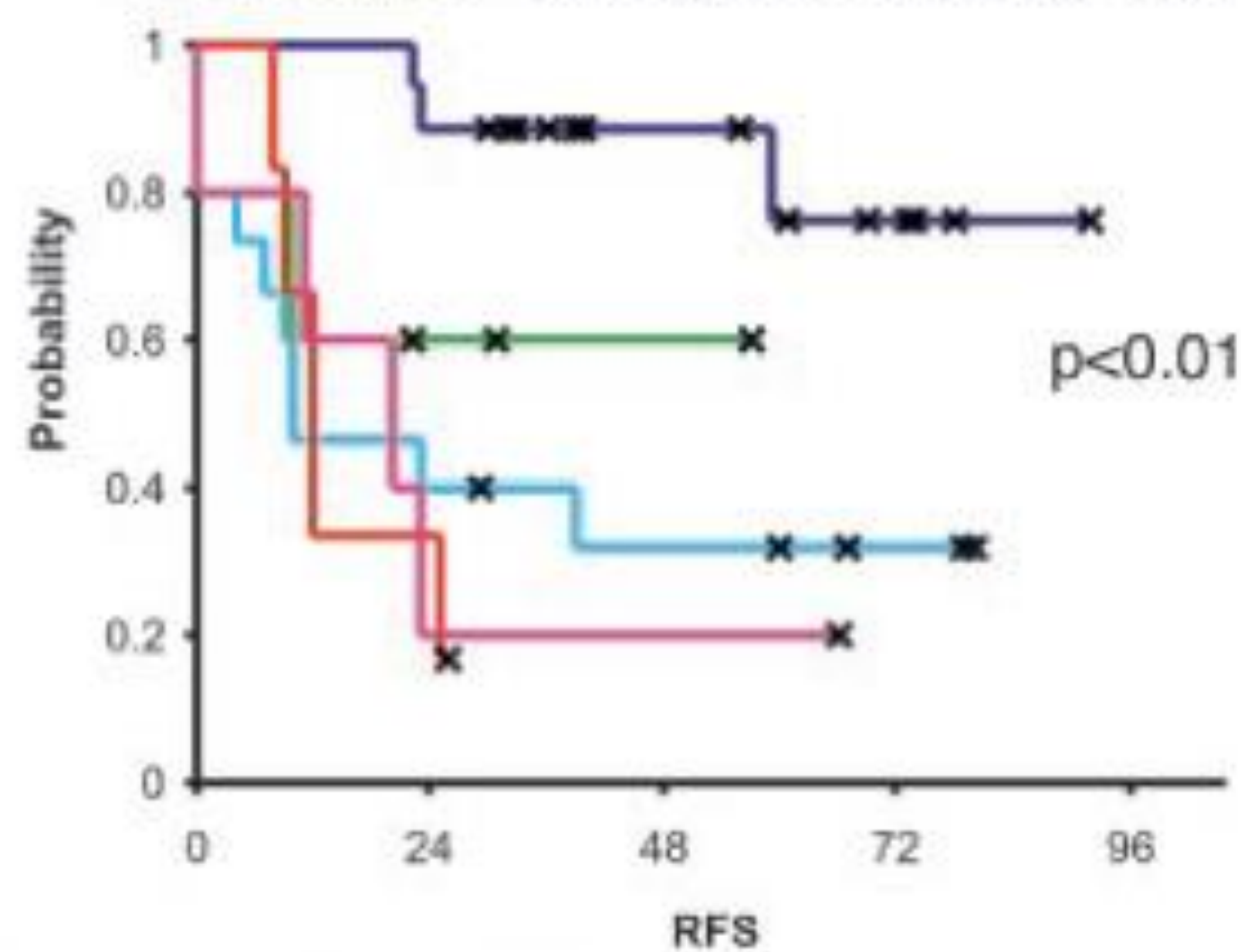
X Censored, — Lum A, — Lum B+C, — NorB-like, — Basal, — ERBB2+

Melhorar prognóstico dos TN?

A 5 tumor subtypes (based upon Fig 1)



B 5 tumor subtypes (based upon Fig 1)



X Censored, Lum A, Lum B+C, NorB-like, Basal, ERBB2+



A arte da Oncologia deve ser aplicada sempre que necessário e, mais importante, deve ser estendida a todos os pacientes, tanto do sistema público quanto da saúde suplementar.

Não se pode fazer arte sem conhecer profundamente a ciência que está envolvida nas decisões.

Obrigada!

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