RAGMA 23

16ª Revisión Anual GEICAM de Avances en Cáncer de Mama

Realidades y esperanzas

Avances en tratamiento de la enfermedad metastásica: Enfermedad con (sobre)expresión de HER2

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Organizado por:

GEICAM investigación en cáncer de mama

DISCLOSURES

Conflictos de interés:

- Advisory role: AstraZeneca, Lilly, Daichi Sankyo
- Consultant/speaker: Lilly, Novartis, Pfizer, AstraZeneca, Roche, Pierre Fabre

ALGORITMO TERAPÉUTICO DEL CÁNCER DE MAMA AVANZADO HER2-POSITIVO

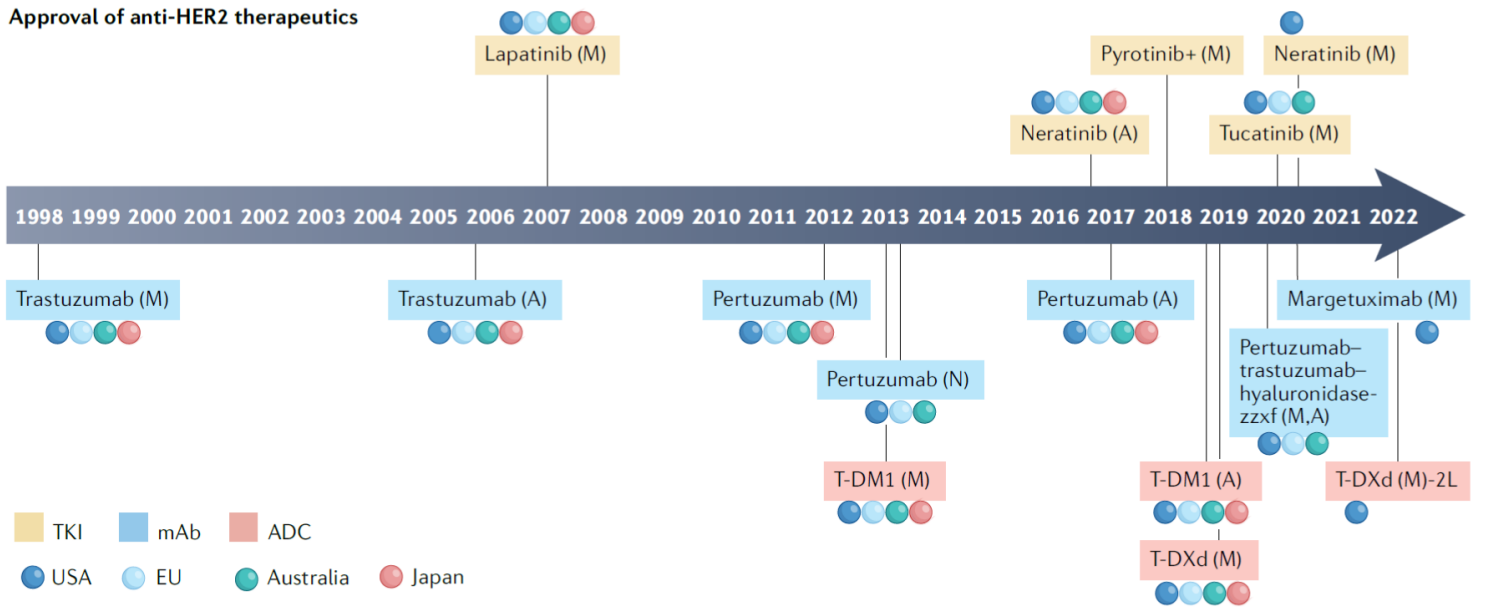


Fig. 1 | Evolution of HER2 as a biomarker and target for treatment for breast cancer. Timeline of preclinical discovery milestones for HER2 biology and regulatory approval for anti-HER2 therapies. A, adjuvant setting; M, metastatic setting; N, neoadjuvant setting; +, approved in China only; *, M. Bishop and H. Varmus awarded Nobel Prize in 1989 for this discovery; **, S. Cohen and R. Levi-Montalcini awarded Nobel Prize in 1986 for discovery of growth factors and their receptors.

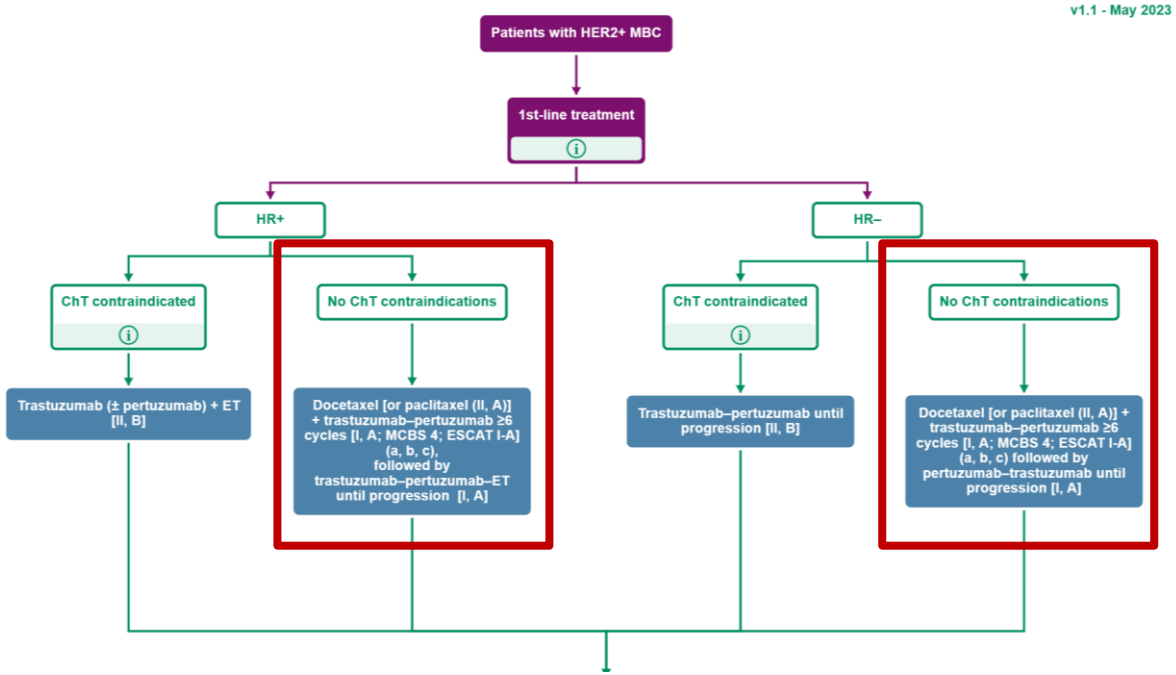
Swain S et al. Nat Rev Drug Discov 2023

2015

Schott A. ASCO 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

2015

2023

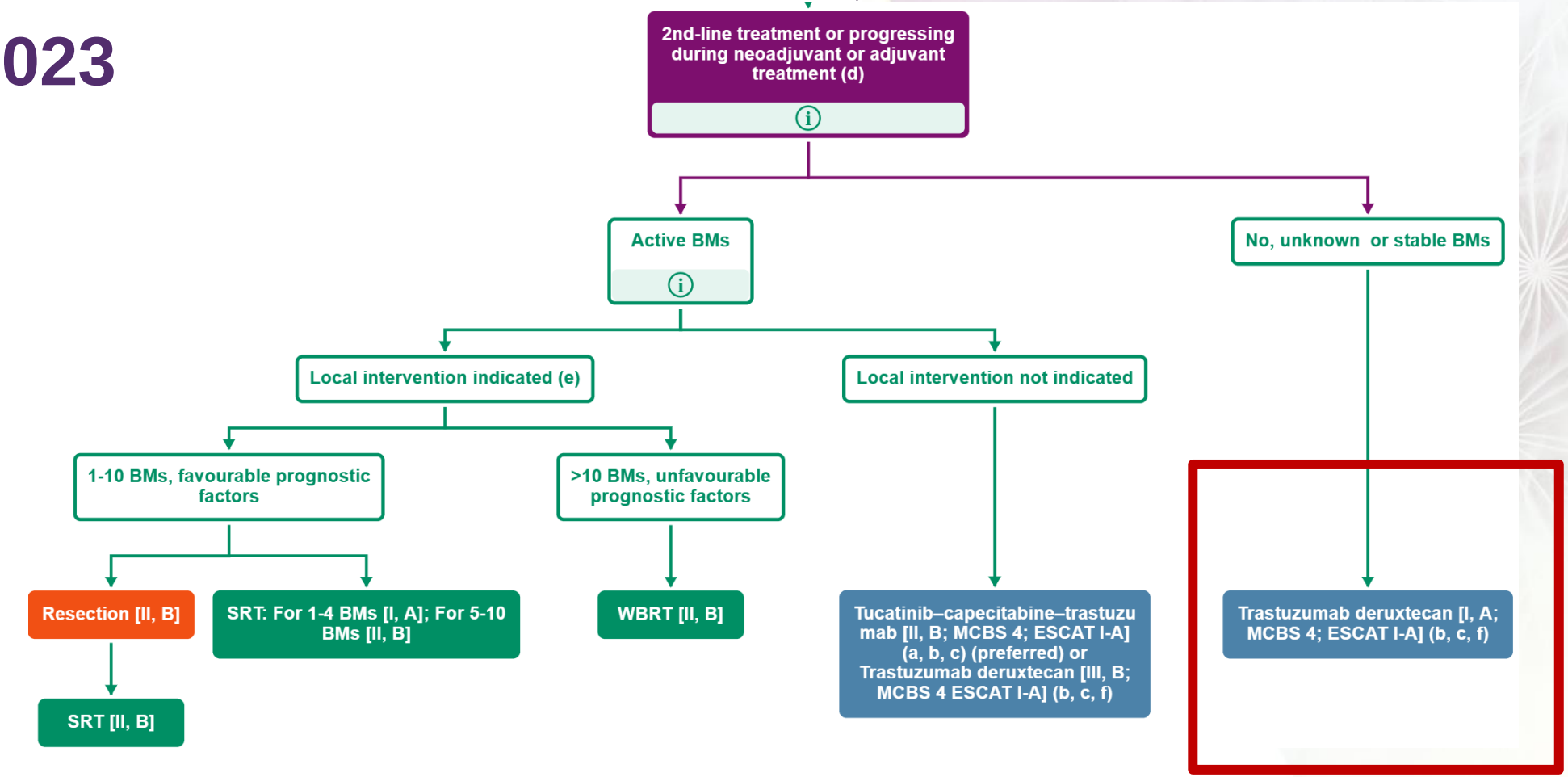


Schott A. ASCO 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

2015

Taxane + trastuzumab+pertuzumab → T-DM1 → Other chemo + trastuzumab -or- capecitabine + lapatinib

2023



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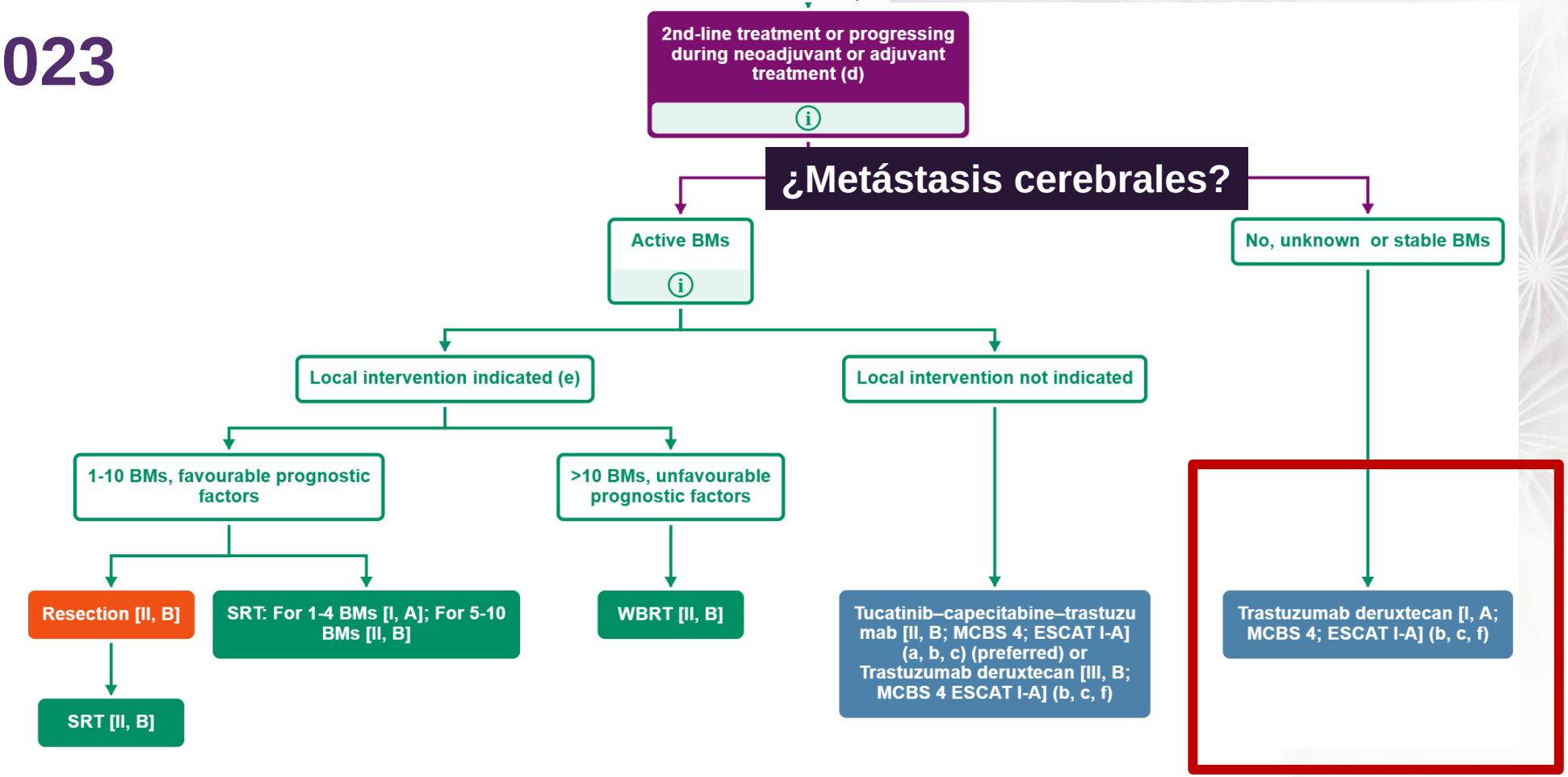

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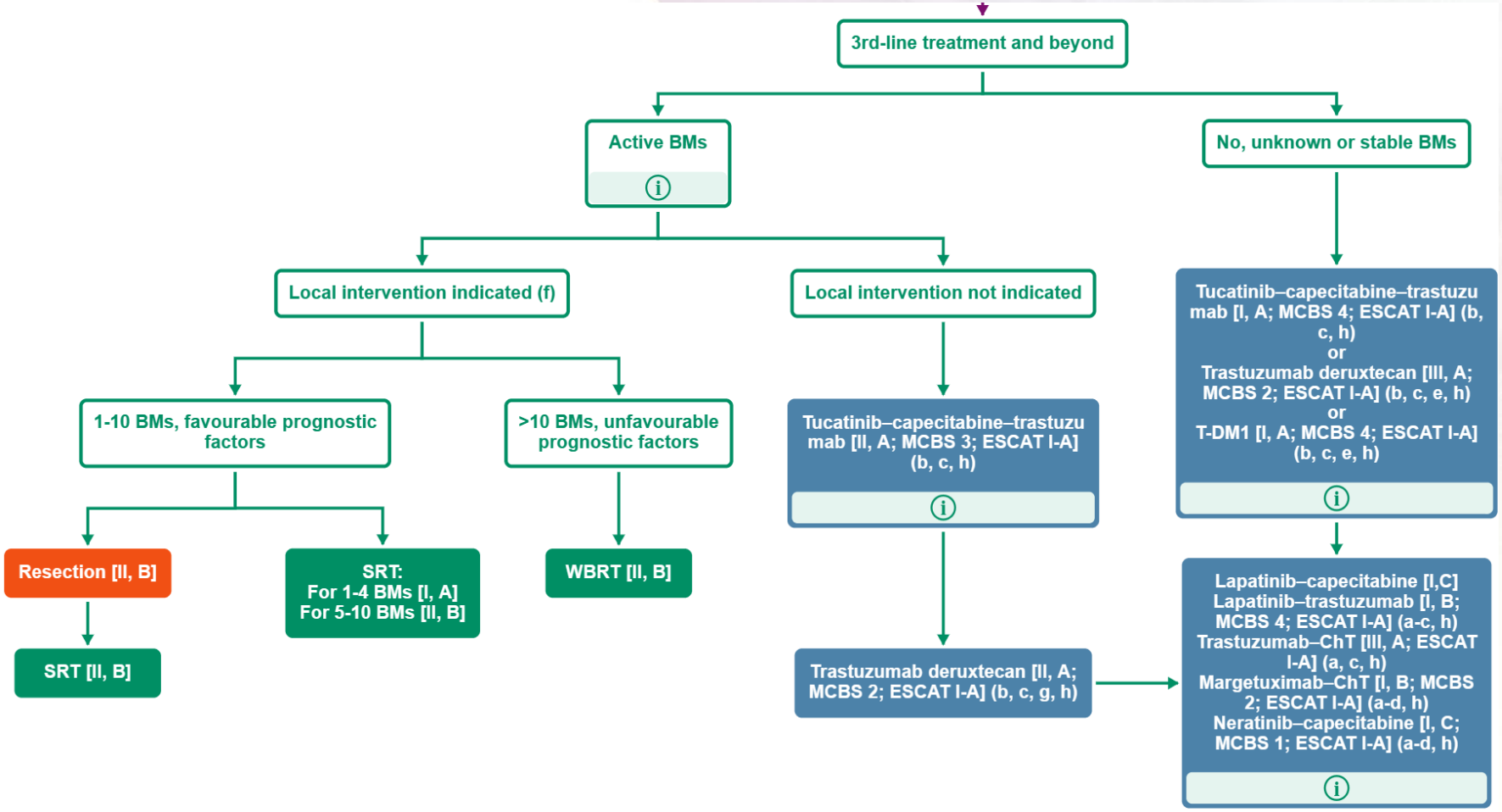
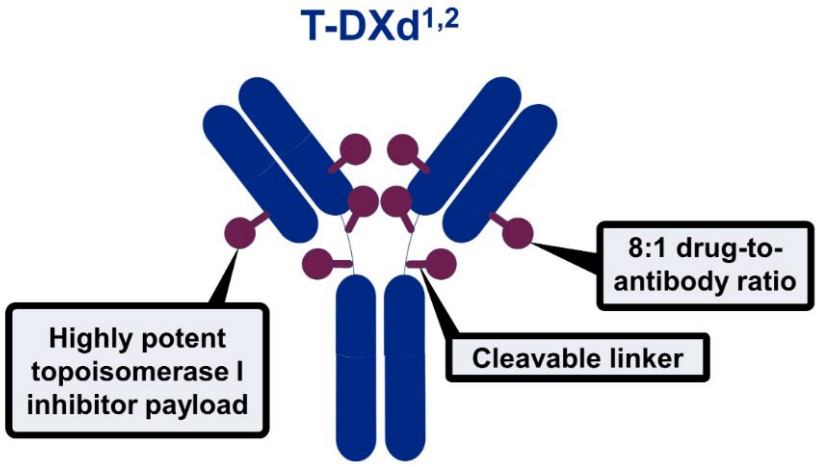
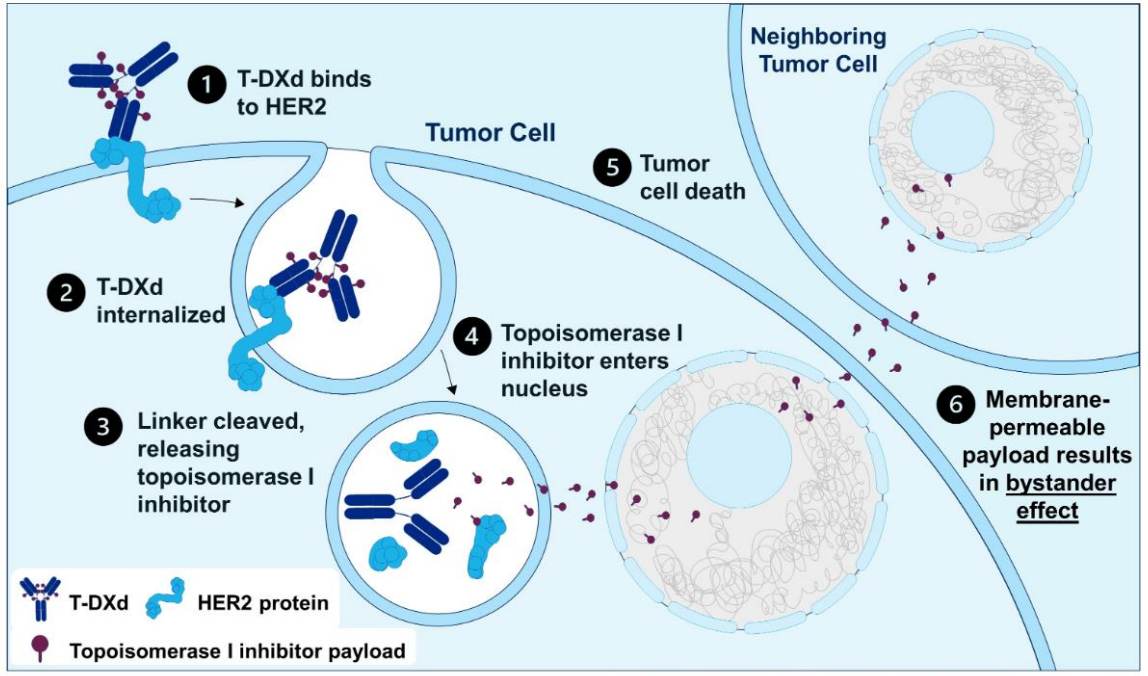


Schott A. ASCO 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

Trastuzumab deruxtecan



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

Modi S. ASCO 2022

¿Cuál es el beneficio de trastuzumab deruxtcan en cada uno de los escenarios?

	"2ª línea"
	DESTINY-Breast03
	Trastuzumab-deruxtecan vs TDM-1
Mediana de líneas	1 (0-16)
PFS	28,8 vs 6,8 meses HR=0,33 **Δ 22 meses**
OS	NR HR=0,64
ORR	79,7 vs 34,2%

Cortes J et al. NEJM 2022. Hurvitz S et al. Lancet 2023. André F et al. Lancet 2023. Modi S et al. NEJM 2019. Saura C et al. ESMO 2021

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
  or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

-

Prior Treatment	T-DXd n = 406	TPC n = 202
Prior treatment for BC, n (%)	406 (100)	202 (100)
Prior lines of therapy in the metastatic setting,[a] n (%)		
0	2 (0.5)	0
1	18 (4.4)	12 (5.9)
2	192 (47.3)	92 (45.5)
3	123 (30.3)	63 (31.2)
4	42 (10.3)	13 (6.4)
≥5	29 (7.1)	22 (10.9)
Median number of prior lines of systemic therapy in the metastatic setting,[a] (range)	2 (0-10)	2 (1-8)
Prior systemic cancer therapy, n (%)		
Trastuzumab	404 (99.5)	202 (100)
T-DM1	404 (99.5)	202 (100)
Taxane	386 (95.1)	197 (97.5)
Pertuzumab	318 (78.3)	156 (77.2)
Other systemic therapy	289 (71.2)	157 (77.7)
Hormone therapy	164 (40.4)	87 (43.1)
Anti-HER2 TKI	26 (6.4)	17 (8.4)
Other anti-HER2 therapy (except HER2 TKI)	11 (2.7)	6 (3.0)

-

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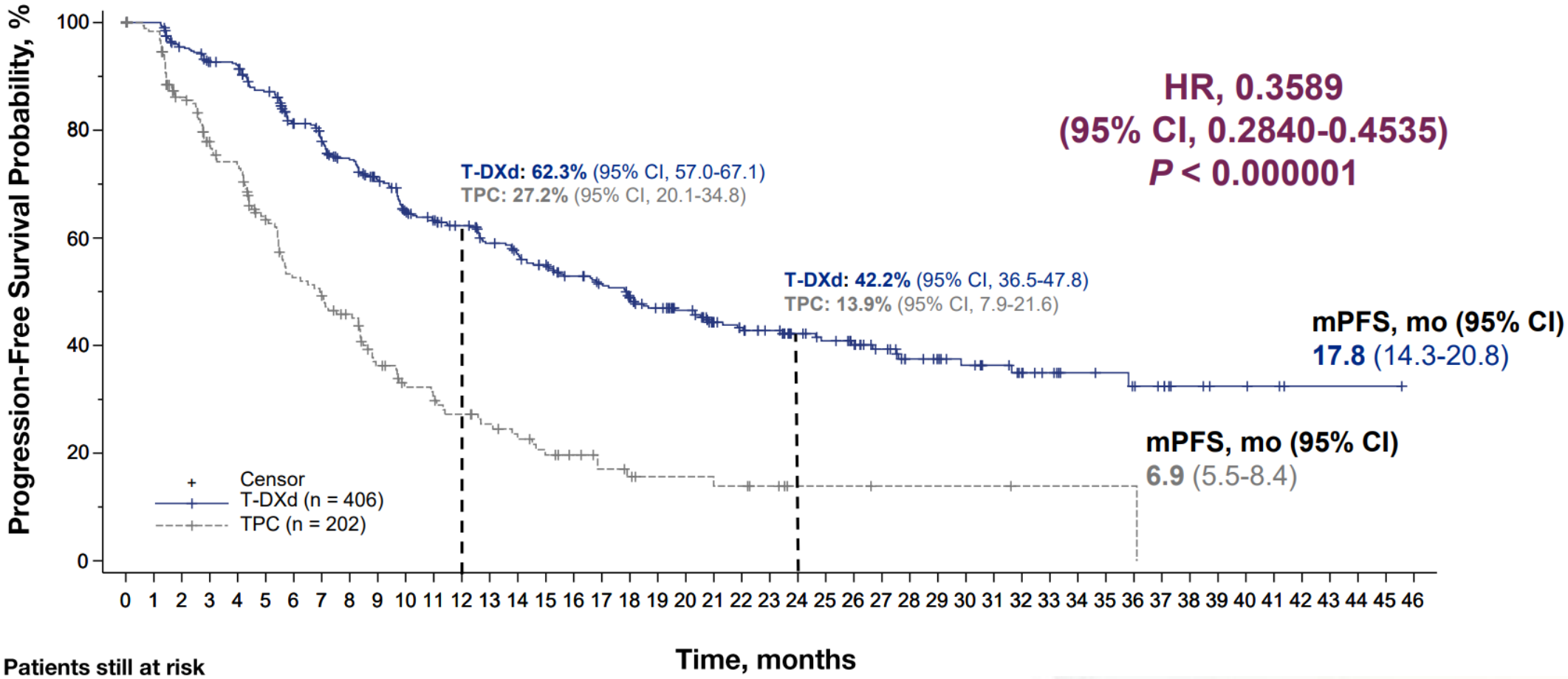
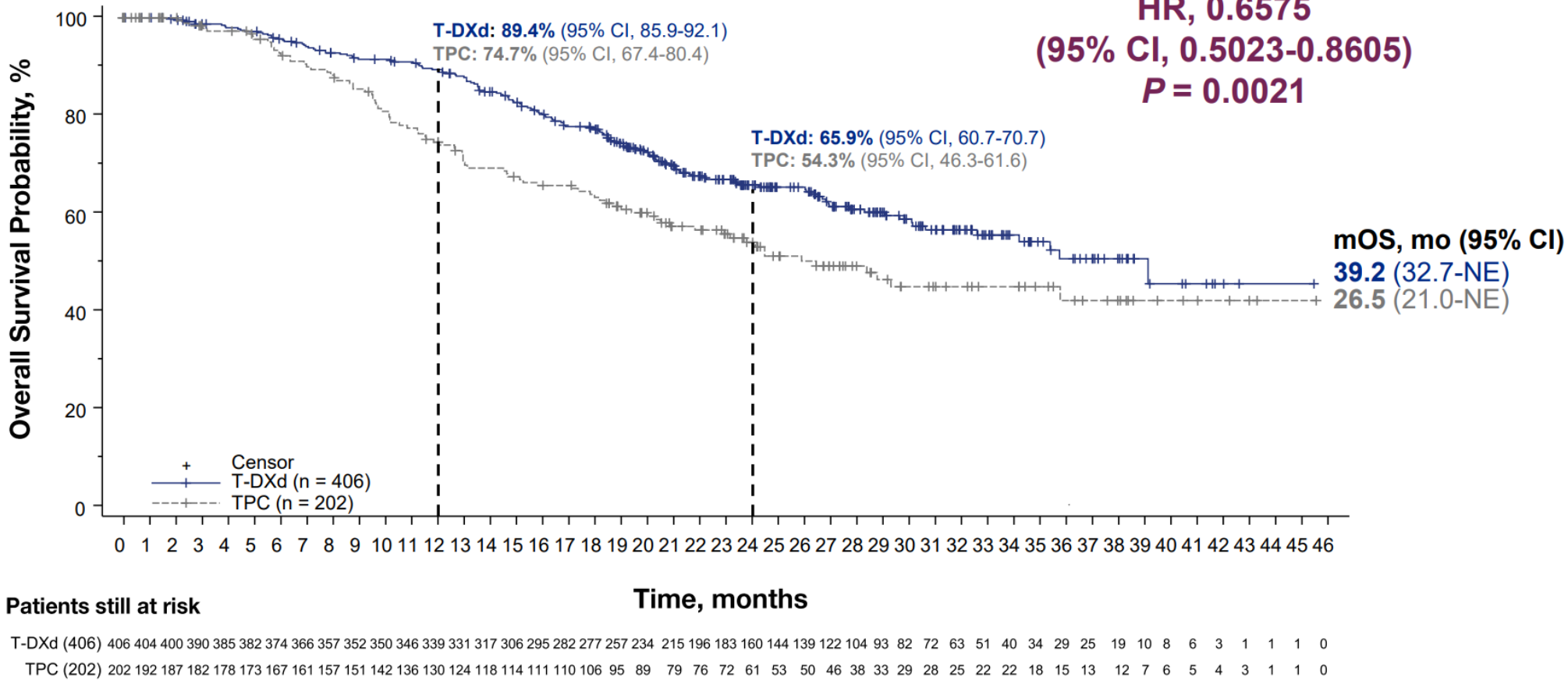
Primary Endpoint: PFS by BICR



Key Secondary Endpoint: OS



In the TPC arm, 190 of 202 (97.4%) patients discontinued therapy. 69.3% (140/202) of patients who discontinued therapy received a new systemic anticancer treatment after discontinuation, with 25.7% (52/202) of patients receiving T-DXd in the post-trial setting

¿Cuál es el beneficio de trastuzumab deruxtcan en cada uno de los escenarios?

	"2ª línea"	"3ª línea"
	DESTINY-Breast03	DESTINY-Breast02
	Trastuzumab-deruxtecan vs TDM-1	Trastuzumab deruxtecan vs capecitabina-trastuzumab/lapatinib
Mediana de líneas	1 (0-16)	2
PFS	28,8 vs 6,8 meses HR=0,33 **Δ 22 meses**	17,8 vs 6,9 meses HR=0,36 **Δ 10,9 meses**
OS	NR HR=0,64	39,2 vs 26,5 meses HR=0,66 **Δ 12,7 meses**
ORR	79,7 vs 34,2%	70% vs 29%

Cortes J et al. NEJM 2022. Hurvitz S et al. Lancet 2023. André F et al. Lancet 2023. Modi S et al. NEJM 2019. Saura

¿Cuál es el beneficio de trastuzumab deruxtcan en cada uno de los escenarios?

	"2ª línea"	"3ª línea"	N línea
	DESTINY-Breast03	DESTINY-Breast02	DESTINY-Breast01
	Trastuzumab-deruxtecan vs TDM-1	Trastuzumab deruxtecan vs capecitabina-trastuzumab/lapatinib	Trastuzumab deruxtecan
Mediana de líneas	1 (0-16)	2	6
PFS	28,8 vs 6,8 meses HR=0,33 **Δ 22 meses**	17,8 vs 6,9 meses HR=0,36 **Δ 10,9 meses**	16,4 meses
OS	NR HR=0,64	39,2 vs 26,5 meses HR=0,66 **Δ 12,7 meses**	28,4 meses
ORR	79,7 vs 34,2%	70% vs 29%	

Cortes J et al. NEJM 2022. Hurvitz S et al. Lancet 2023. André F et al. Lancet 2023. Modi S et al. NEJM 2019. Saura

2023 ASCO ANNUAL MEETING

An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

Ian Krop

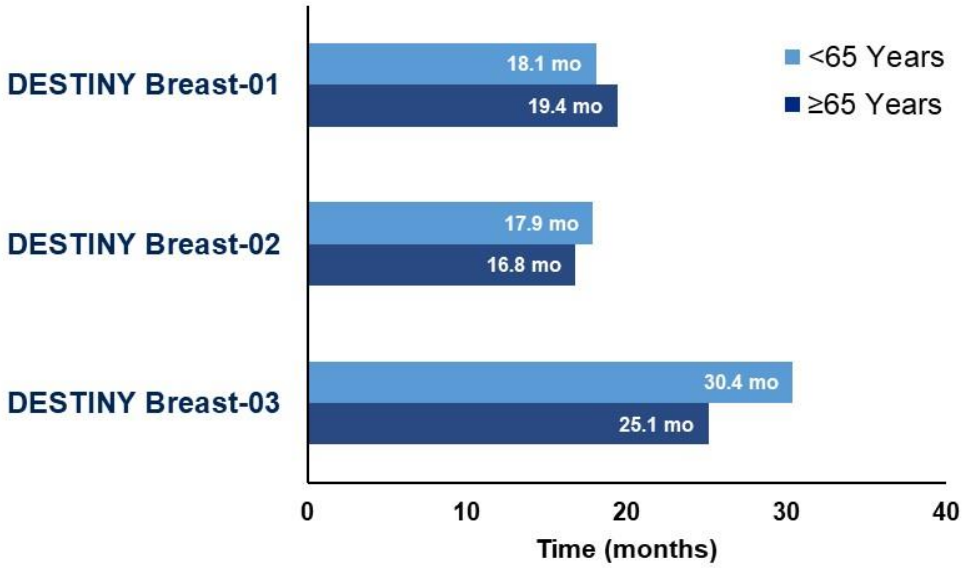
Yale Cancer Center, New Haven, CT, USA

June 5, 2023

Additional authors:
Hans Wildiers, Sara Hurvitz, Javier Cortes, Seock-Ah Im, Hiroji Iwata, Fabrice André, Cristina Saura, Shanu Modi, Sung-Bae Kim, Anton Egorov, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Yingkai Cheng, Yeon Hee Park

Descriptive Efficacy According to Age for T-DXd[a]

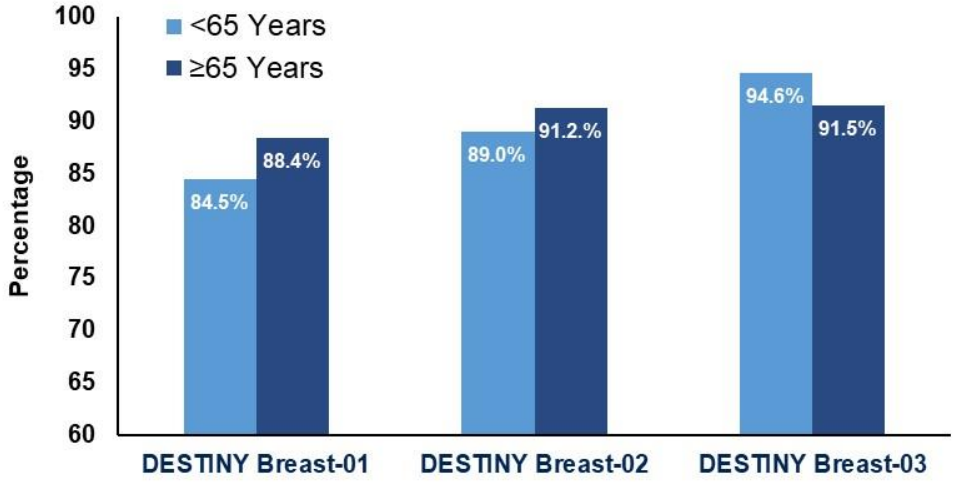
Median Progression Free Survival



Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

12-month Landmark Overall Survival



- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however no formal comparison was made

[a]Efficacy data was not pooled due to bias induced by the heterogeneity of the study population. Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022. mOS, median overall survival; NE, not estimable; NR, not reached; T-DXd, trastuzumab deruxtecan.

Overall Safety Summary[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Median treatment duration, mo (range)	**13.1 (0.7-44.0)**	**12.4 (0.7-45.1)**	**9.0 (0.7-35.6)**	**N/A[b]**	**N/A[b]**	**N/A[b]**	**6.9 (0.7-38.9)**	**8.2 (0.7-38.9)**	**7.7 (2.0-29.4)**
TEAE, n (%)	**665 (99.6)**	**177 (100.0)**	**33 (100.0)**	**148 (94.3)**	**37 (97.4)**	**8 (100.0)**	**194 (95.1)**	**55 (96.5)**	**8 (100.0)**
Drug-related	653 (97.8)	176 (99.4)	33 (100.0)	144 (91.7)	36 (94.7)	8 (100.0)	178 (87.3)	50 (87.7)	8 (100.0)
TEAEs grade ≥3, n (%)	**358 (53.6)**	**116 (65.5)**	**17 (51.5)**	**68 (43.3)**	**18 (47.4)**	**6 (75.0)**	**100 (49.0)**	**35 (61.4)**	**4 (50.0)**
Drug-related	291 (43.6)	96 (54.2)	13 (39.4)	48 (30.6)	12 (31.6)	5 (62.5)	82 (40.2)	28 (49.1)	3 (37.5)
Serious TEAEs, n (%)	**162 (24.3)**	**57 (32.2)**	**10 (30.3)**	**39 (24.8)**	**7 (18.4)**	**1 (12.5)**	**33 (16.2)**	**25 (43.9)**	**4 (50.0)**
Drug-related	77 (11.5)	29 (16.4)	5 (15.2)	13 (8.3)	2 (5.3)	1 (12.5)	11 (5.4)	9 (15.8)	2 (25.0)
TEAEs associated with drug discontinuation, n (%)	**125 (18.7)**	**45 (25.4)**	**8 (24.2)**	**15 (9.6)**	**4 (10.5)**	**1 (12.5)**	**13 (6.4)**	**11 (19.3)**	**3 (37.5)**
Drug-related	100 (15.0)	42 (23.7)	8 (24.2)	8 (5.1)	2 (5.3)	1 (12.5)	9 (4.4)	8 (14.0)	2 (25.0)
TEAEs associated with dose reduction, n (%)	**163 (24.4)**	**51 (28.8)**	**10 (30.3)**	**67 (42.7)**	**22 (57.9)**	**7 (87.5)**	**23 (11.3)**	**15 (26.3)**	**2 (25.0)**
Drug-related	156 (23.4)	47 (26.6)	8 (24.2)	67 (42.7)	22 (57.9)	7 (87.5)	23 (11.3)	15 (26.3)	2 (25.0)
TEAEs associated with dose interruption, n (%)	**302 (45.2)**	**94 (53.1)**	**15 (45.5)**	**73 (46.5)**	**17 (44.7)**	**5 (62.5)**	**53 (26.0)**	**23 (40.4)**	**3 (37.5)**
Drug-related	226 (33.8)	74 (41.8)	11 (33.3)	61 (38.9)	15 (39.5)	5 (62.5)	30 (14.7)	15 (26.3)	3 (37.5)
TEAEs associated with death, n (%)	**17 (2.5)**	**10 (5.6)**	**0**	**6 (3.8)**	**1 (2.6)**	**0**	**4 (2.0)**	**2 (3.5)**	**1 (12.5)**
Drug-related	4 (0.6)	3 (1.7)	0	0	0	0	0	0	0

[a]Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022. [b]Not reported for TPC as this was a combination regimen; median treatment duration, mo (range), for <65, ≥65, and ≥75 was 4.1 (0.1-43.0), 4.7 (1.4-22.7), and 13.3 (4.1-22.7) for trastuzumab; 4.5 (0.1-43.0), 4.9 (0.7-28.7), and 9.8 (2.6-22.7) for capecitabine; 4.6 (0.4-23.7), 5.2 (0.7-28.7), and 8.0 (2.6-11.5) for lapatinib.
mo, months; N/A, not applicable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer

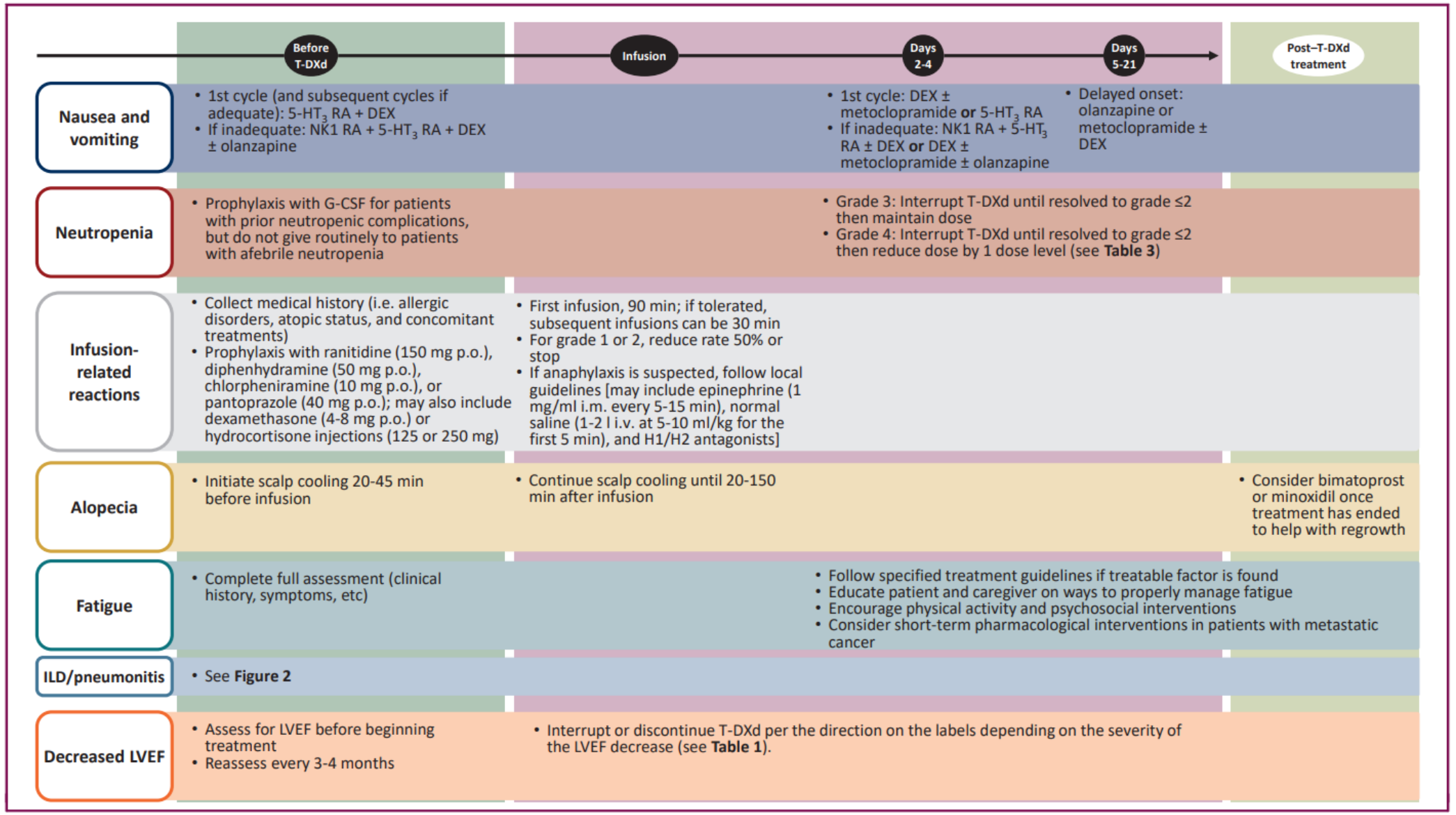


Figure 1. Overview of management of T-DXd-related adverse events.

Rugo H et al. ESMO Open 2022

El algoritmo terapéutico ha cambiado, las poblaciones de estudio no se ajustan a la realidad. ¿qué datos tenemos en el escenario actual?

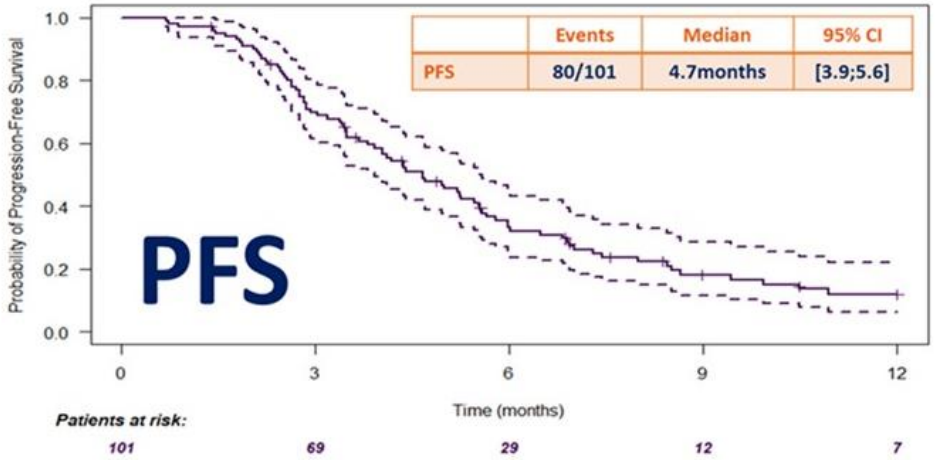
Efficacy of Tucatinib+Trastuzumab+Capecitabine (TTC) after Trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer. A French multicentre retrospective study.

Characteristics, n (%)		n=101
Female		101 (100%)
Age (years), median (range)		56 (30-84)
Age	<65 years	79 (78.2%)
	≥65 years	22 (21.8%)
Stage IV at initial diagnosis		34 (34.3%)
Hormone receptor status	ER and/or PR-positive	72 (71.3%)
	ER and PR-negative	29 (28.7%)
Prior lines of therapy, median (range)	Overall	5 (2-16)
	Metastatic setting	4 (2-15)
Previous therapies	Trastuzumab	100 (99.0%)
	Pertuzumab	82 (81.2%)
	T-DM1	94 (93.1%)
	Lapatinib	33 (32.7%)
	T-DXd	101 (100.0%)
	Median duration of T-DXd (months)	8.9 (1.4-31.4)
Brain metastases		39 (38.6%)
TTC immediately after T-DXd		86 (85.1%)
Reason for T-DXd discontinuation	Progression	82 (81.1%)
	Toxicity	18 (17.8%)
	Unknown	1 (1.1%)

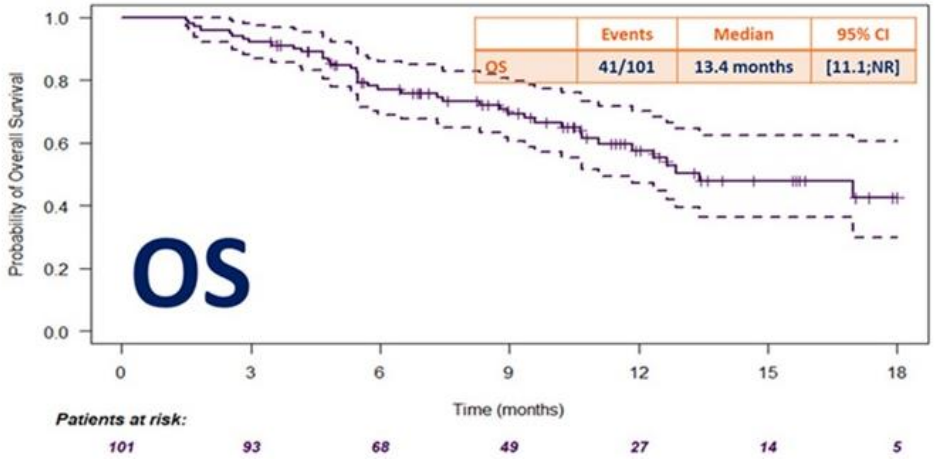
Frenel JS et al. ASCO 2023

Efficacy of Tucatinib+Trastuzumab+Capecitabine (TTC) after Trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer. A French multicentre retrospective study.

Median Follow-up: 11.6 months [10.5-13.4]



Estimated PFS at 6 months (95% CI)
33.1% [24.8;44.3]
Estimated PFS at 12 months (95% CI)
11.9% [6.4;22.1]



Estimated OS at 6 months (95% CI)
77.0% [69.0;86.0]
Estimated OS at 12 months (95% CI)
57.5% [47.2;66.1]

Frenel JS et al. ASCO 2023

CÁNCER DE MAMA HER2-POSITIVO CON METÁSTASIS CEREBRALES

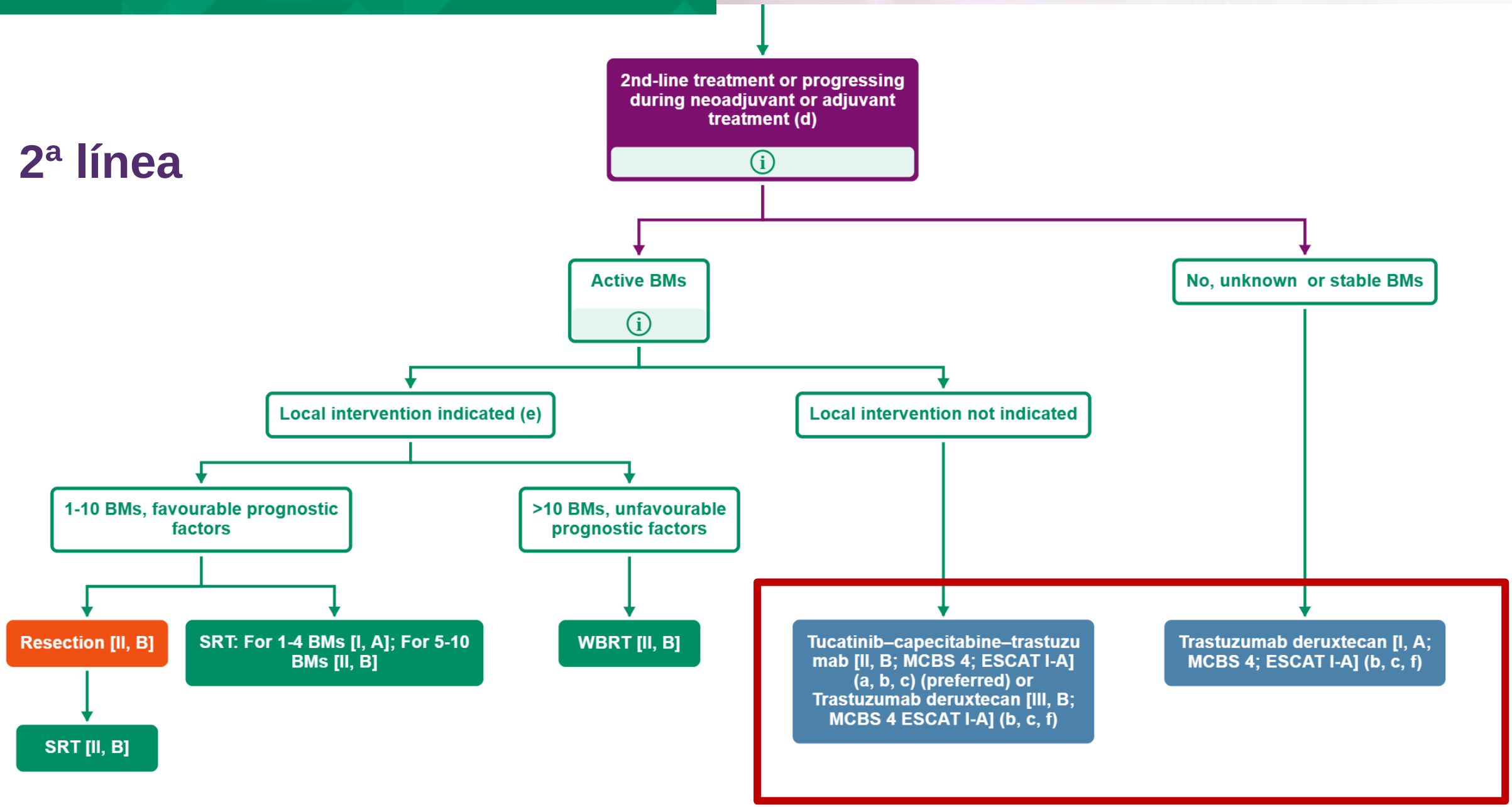
Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Guideline Update

Clinical question 3 Should patients with HER2-positive breast cancer be screened for development of brain metastases?	***Recommendation 10.1 (screening).*** If a patient does not have a known history or symptoms of brain metastases, *there are insufficient data to recommend for or against* performing routine surveillance with brain MRI. *Clinicians and patients may discuss options using shared decision-making processes*	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Weak
	Recommendation 10.2. Clinicians should have a low threshold for performing diagnostic brain MRI testing in the setting of any neurologic symptoms suggestive of brain involvement, such as new-onset headaches, unexplained nausea or vomiting, or change in motor or sensory function	Type: Formal consensus Evidence quality: Low Strength of recommendation: Strong

Ramakrishna N et al. JCO 2022

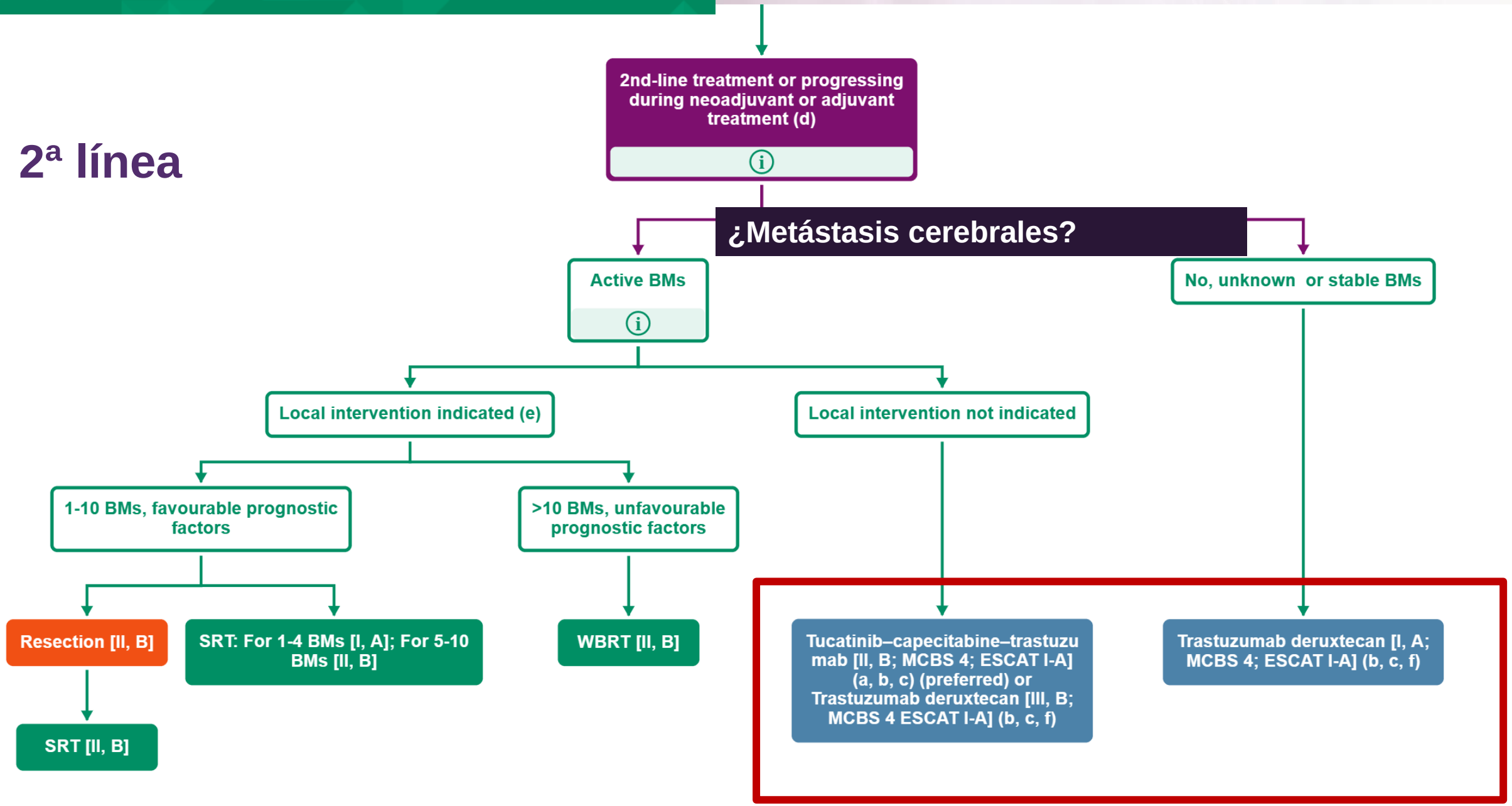
ESMO Metastatic Breast Cancer Living Guideline

2ª línea



ESMO Metastatic Breast Cancer Living Guideline

2ª línea



Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases

Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial

N=612

≈ 50% metástasis cerebrales (n=291)

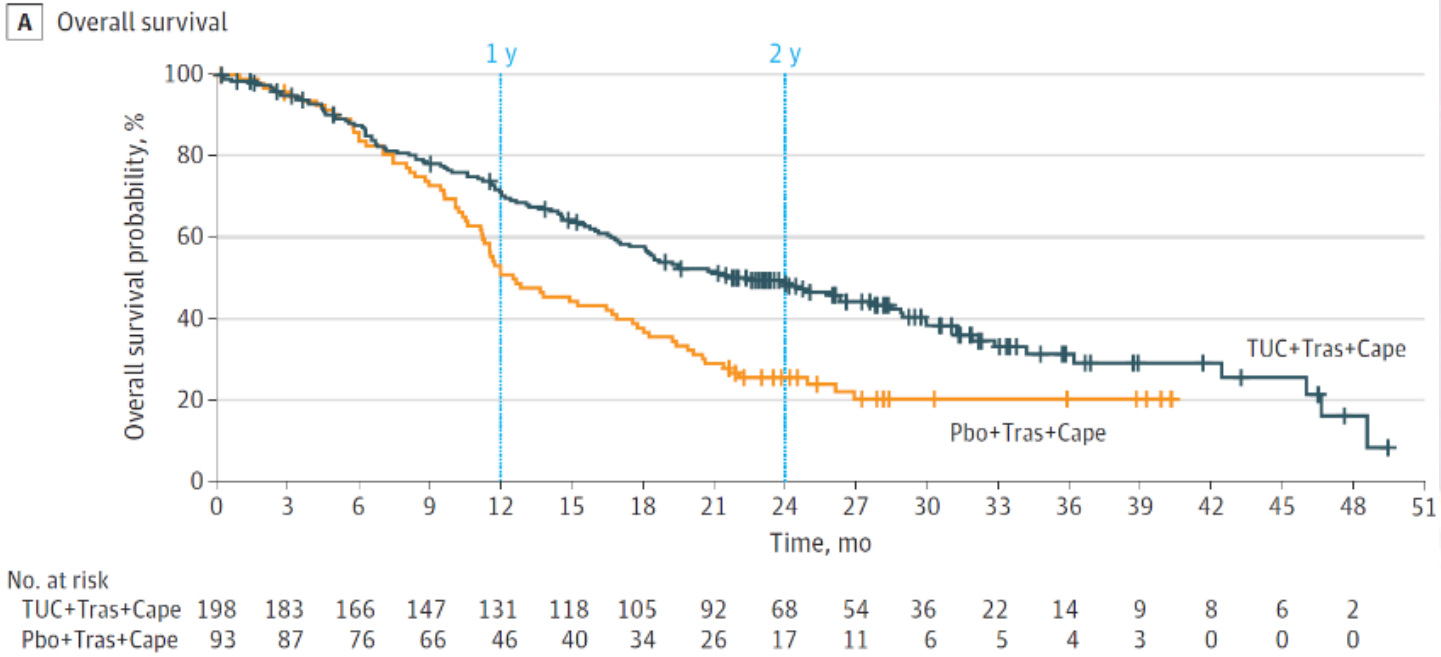
- 40% tratadas y estables
- 37% en progresión tras tratamiento local
- 23% no tratadas

Table. Confirmed Intracranial Responses in Patients With Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Intracranial response	Tucatinib combination (n = 55)[a]	Placebo combination (n = 20)[b]
Patients with objective response of confirmed complete response or partial response, No.	26	4
Confirmed ORR-IC, % (95% CI)	47.3 (33.7-61.2)	20.0 (5.7-43.7)
DOR-IC, median (95% CI), mo[c]	8.6 (5.5-10.3)	3.0 (3.0-10.3)

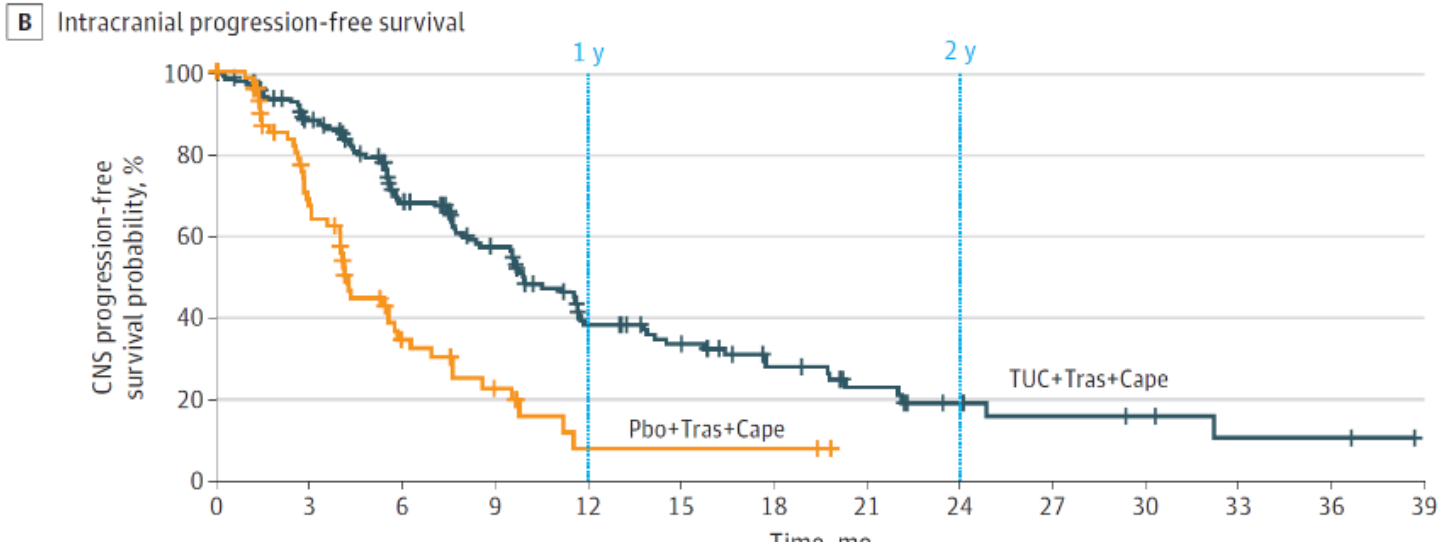
Lin N et al. . JCO 2020. Lin N et al. JAMA Oncol 2023

Figure 2. Efficacy of Tucatinib Combination Therapy in Patients With Brain Metastases



No. at risk

TUC+Tras+Cape	198	183	166	147	131	118	105	92	68	54	36	22	14	9	8	6	2
Pbo+Tras+Cape	93	87	76	66	46	40	34	26	17	11	6	5	4	3	0	0	0



Mediana de seguimiento de 29,6 meses.

Mediana de SG 21,6 vs 12,5 meses (beneficio absoluto 9,1 meses)

- Metástasis cerebrales activas: 21,4 vs 11,8 meses

Mediana de SLP a nivel intracraneal: 9,9 vs 4,2 meses

- Metástasis cerebrales activas: mSLP 9,5 vs 4,1 meses
- Metástasis cerebrales estables: mSLP 13,9 vs 5,6 meses

Mediana de tiempo hasta la aparición de nuevas lesiones cerebrales: 24,9 frente a 13,8 meses.

Lin N et al. JAMA Oncol 2023

EVIDENCIA CON TRASTUZUMAB DERUXTECAN

Metástasis tratadas y estables

Incluidas en estudios DESTINY-Breast

Metástasis no tratadas o en progresión

No incluidas en estudios DESTINY-Breast
Ensayo DEBBRAH
Ensayo TUXEDO

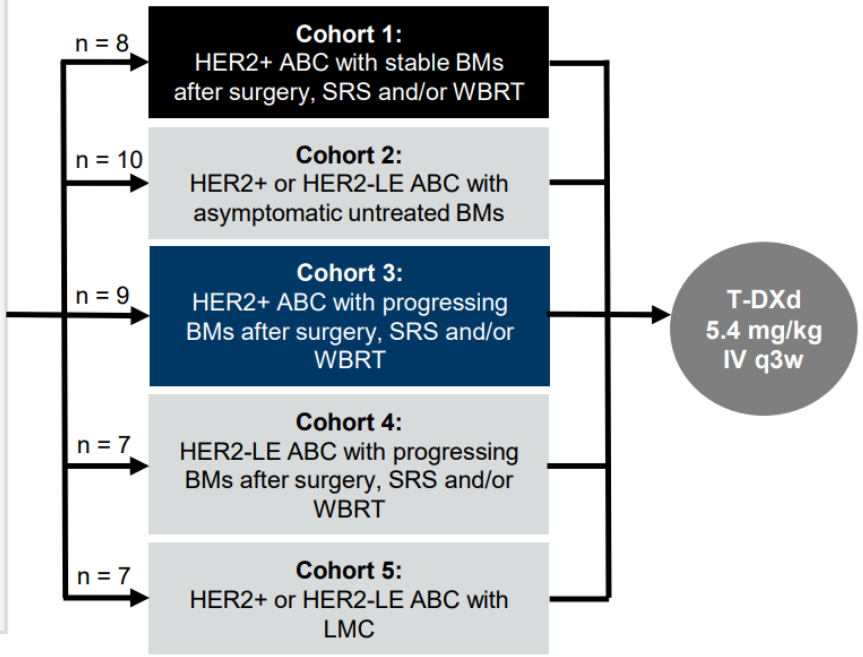
DEBBRAH: Phase 2 Study of T-DXd in Patients With HER2+ or HER2-LE ABC and CNS Involvement—Preliminary Results

Study Design and Population:

DEBBRAH: IIS, multicenter, open-label, single-arm, five-cohort phase 2 trial

Population

- HER2+ or HER-LE ABC with stable, progressing, or untreated BMs and/or LMC
- ECOG PS 0 or 1 (0-2 for cohort 5)
- Patients with HER2+ ABC: prior treatment with a taxane and ≥ 1 line of anti-HER2 therapy in the metastatic setting
- Patients with HER2-LE ABC and:
  - HR-: ≥ 1 prior regimen of CT in the metastatic setting
  - HR+: 1 prior line of ET and ≥ 1 prior regimen of CT in the metastatic setting
- Cohorts 2, 3, 4: measurable brain disease on T1-weighted, gadolinium-enhanced MRI
- Cohort 5: LMC with CSF+ cytology



Primary endpoints	
Cohort 1	16-week PFS per RANO-BM and RECIST 1.1
Cohort 3	ORR-IC per RANO-BM
Secondary endpoints	
Cohort 1 and **Cohort 3**	CNS-PFS, CBR-IC, TTR-IC, DOR-IC, IC stabilization, and best percentage of change in tumor burden per RANO-BM; PFS, ORR, CBR, TTR, DOR per RECIST 1.1; OS; and safety per NCI-CTCAE v5.0
Cohort 1 only	ORR-IC
Exploratory endpoints	
• Evaluate patient reported outcomes using questionnaires • Evaluate predictive and/or prognostic factors on blood and/or tissue biopsies	

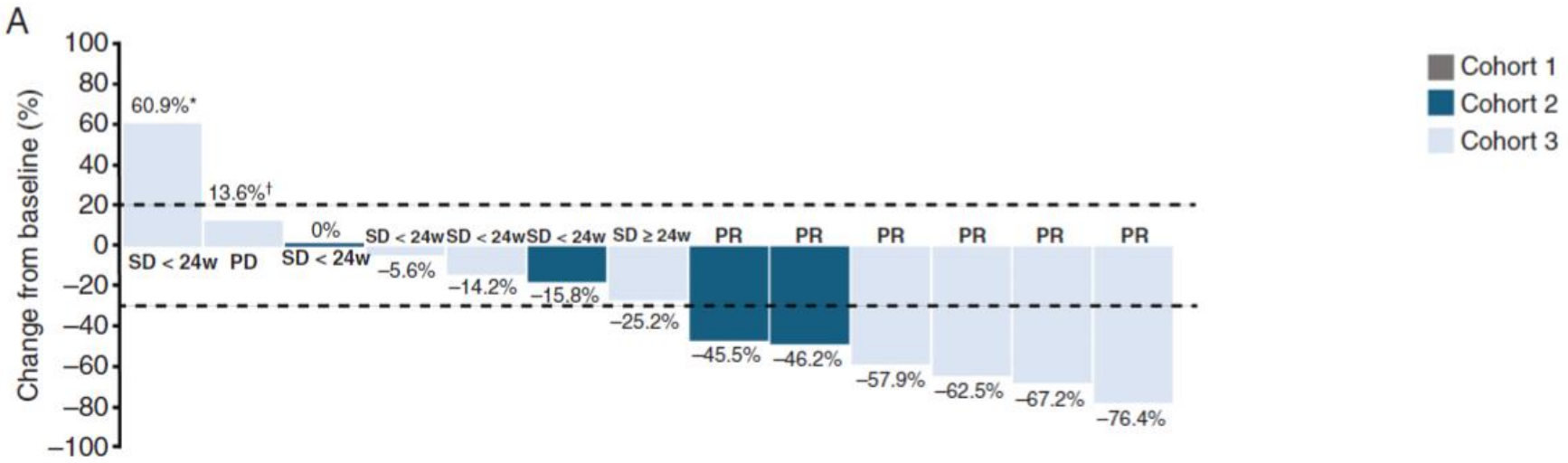
- Data cutoff date: September 15, 2021
- Time from enrollment to the last patient follow-up, median (range): 8.5 months (4.5-12.6) in cohort 1 and 8.8 months (2.1-10.8) in cohort 3

Click for abbreviations

Vaz Batista M, et al. SABCS 2021. Abstract 2231.

Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: The DEBBRAH trial

Actividad a nivel intracraneal cohortes 1-3



ORR-IC entre los pacientes con enfermedad medible: 66,7%
CBR-IC 72,2%

Cohorte 1 (sin PGR tras tratamiento local):

- 87,5% pacientes sin PGR intracraneal a las 16 semanas

Cohorte 2 (metástasis cerebrales no tratadas, n=4):

- ORR 50%
- No PD IC

Cohorte 3 (metástasis cerebrales en PGR tras tratamientos locales, n=9):

- ORR 44,4%
- 11,1% EE > 24 semanas
- 33,3% EE < 24 semanas
- 11,1% PD

Pérez-García JM et al. Neurooncology 2023

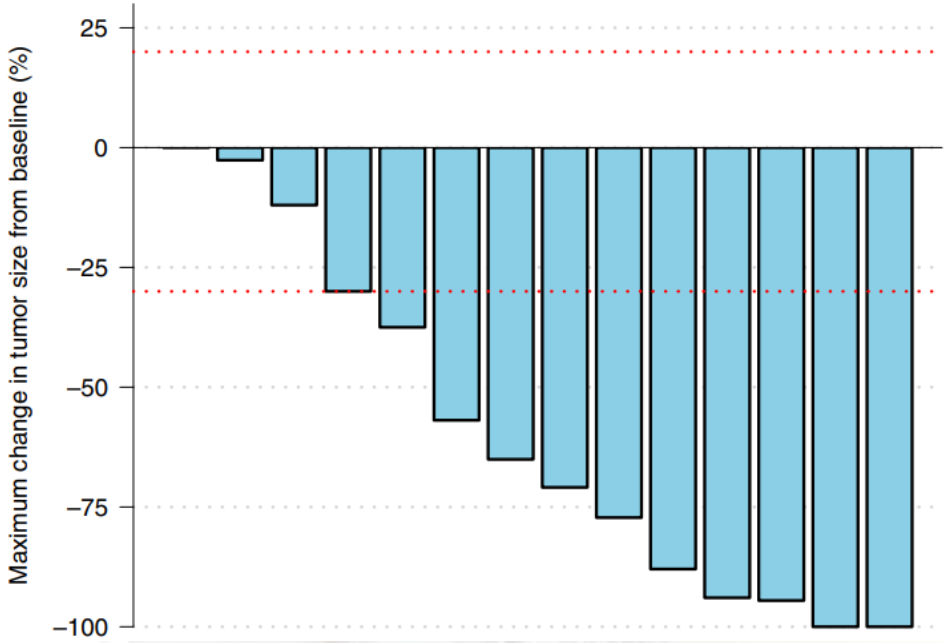
TUXEDO TRIAL

TUXEDO-1 (NCT04752059)

Inclusion/exclusion criteria

- Histologically confirmed HER2+ breast cancer
- Radiologically documented metastatic disease
- Newly diagnosed brain metastases or brain metastases progressing after prior local therapy
- Measurable disease (RANO-BM criteria)
- No indication for immediate local treatment
- No indication of leptomeningeal disease
- KPS >70%, ECOG <2
- Indication for systemic anti-HER2 treatment
- Prior exposure to trastuzumab and pertuzumab
- Prior exposure to T-DM1 allowed
- Life expectancy of at least 3 months
- Age >18 years
- LVEF ≥50%

→ Trastuzumab deruxtecan (5.4 mg/kg IV q3w



N= 15 pacientes
- 60% progresión SNC tras tratamientos locales
- 40% sin tratamiento

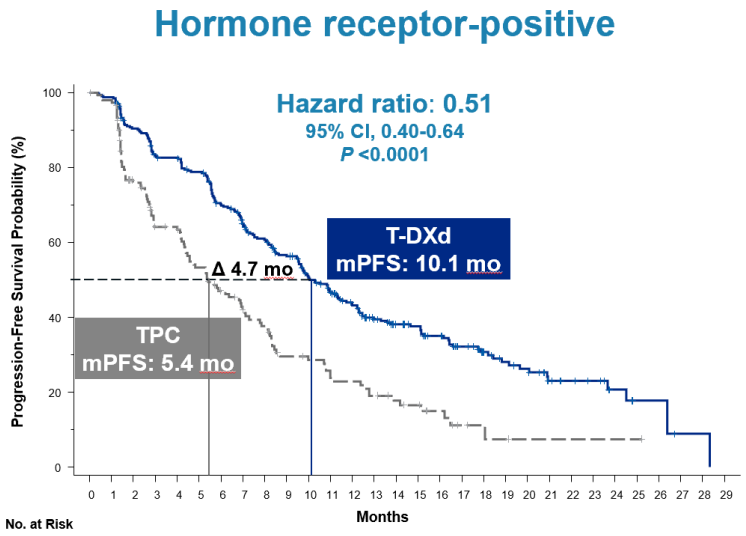
60% TDM-1 previo
Mediana de líneas previas: 2

ORR-IC: 73,3%
CBR-IC: 92,9%
Median PFS 14 meses
Median OS NR.

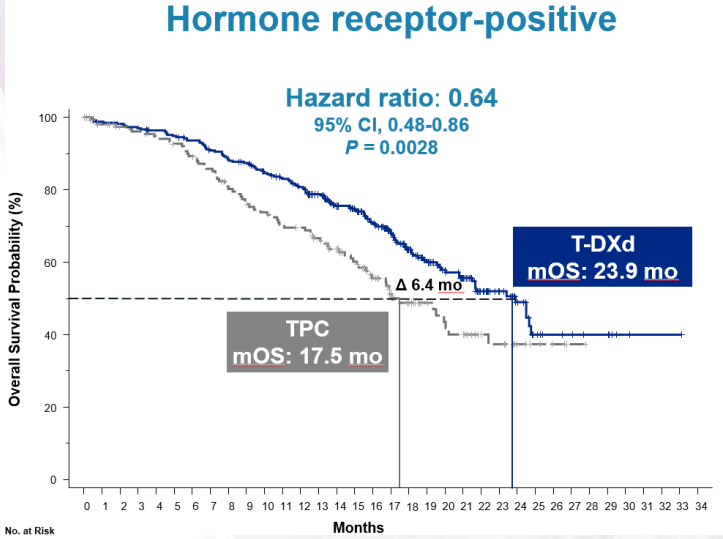
Bartsch R et al. Nature Med 2022

HER2-low, el biomarcador de moda,

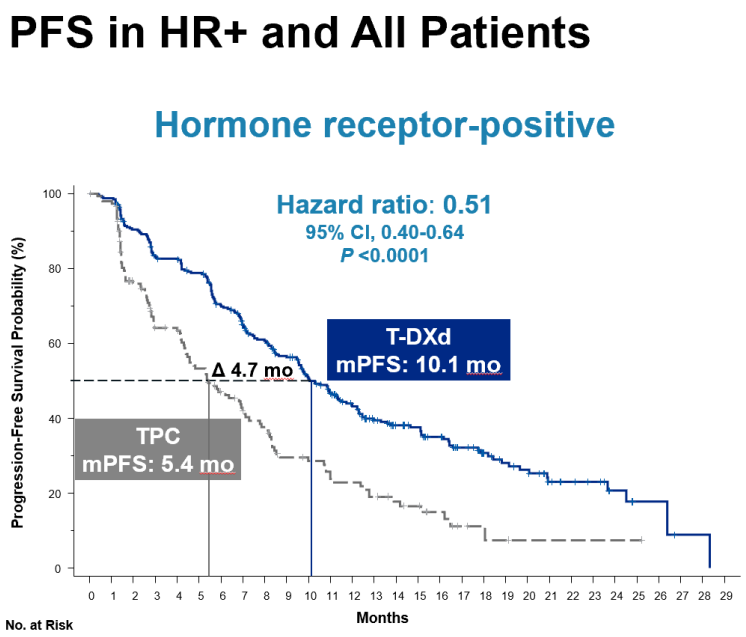
PFS in HR+ and All Patients

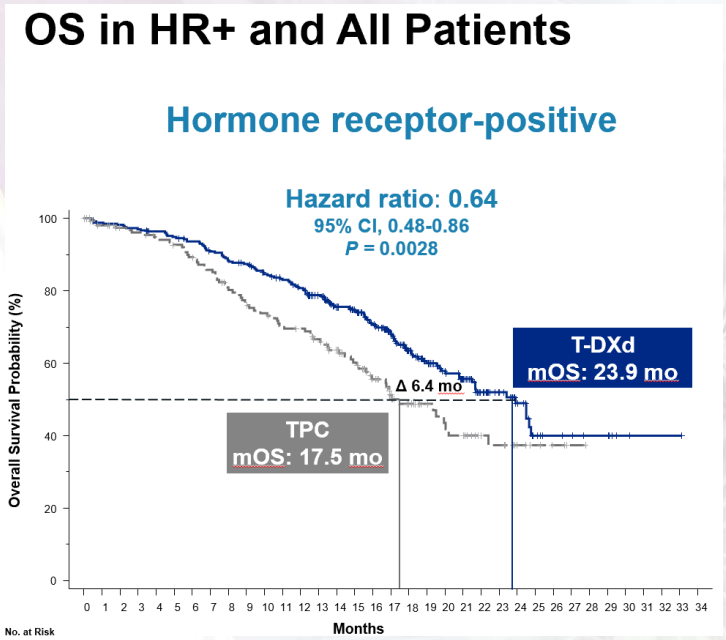


OS in HR+ and All Patients



HER2-low, el biomarcador de moda,

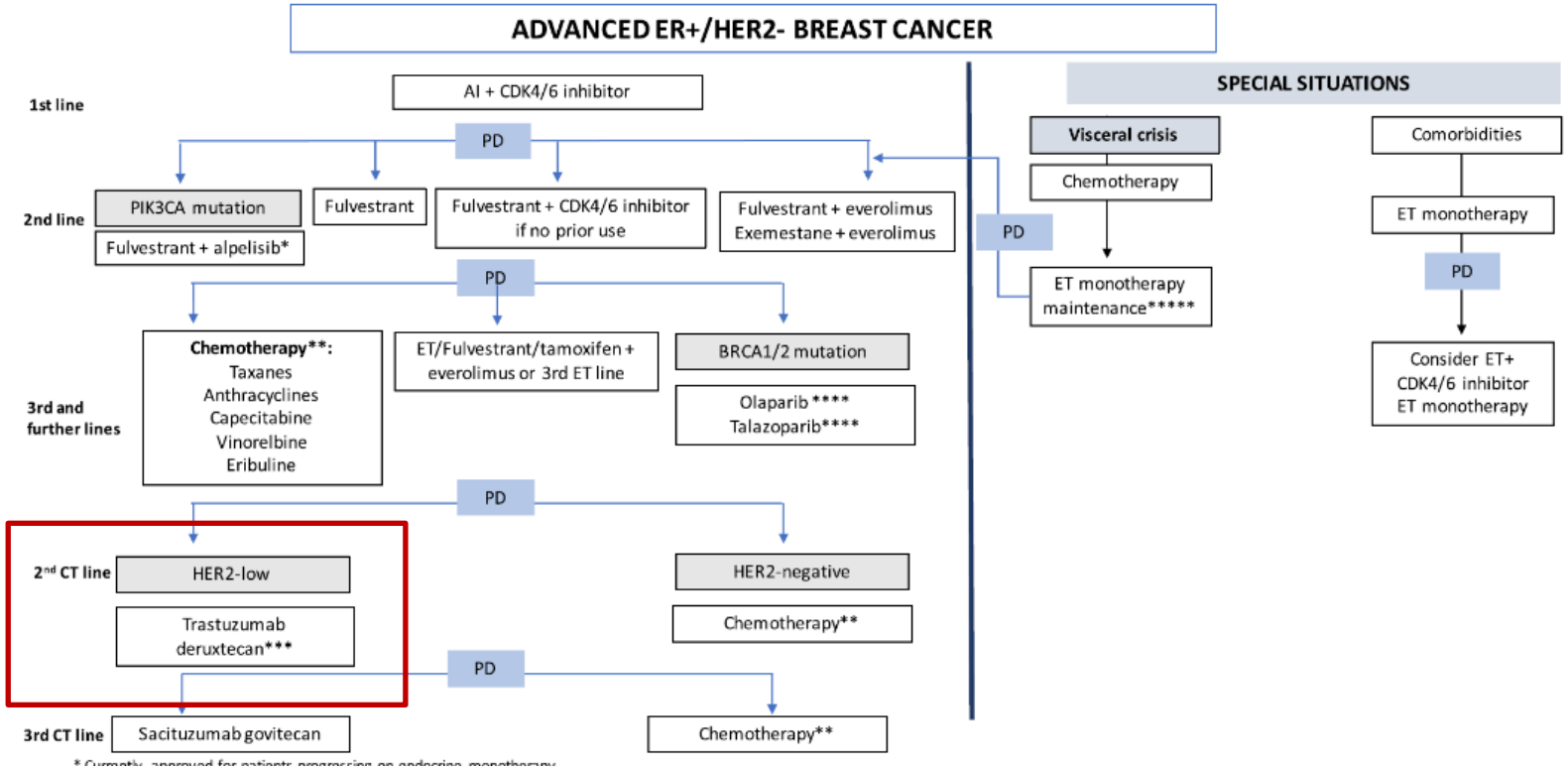




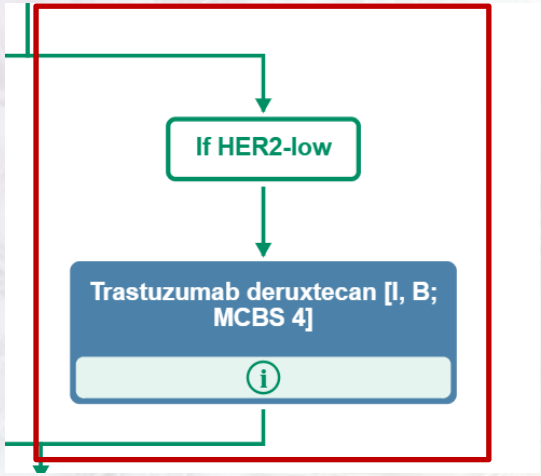
¿pero hasta cuándo?

¿realmente se trata de una entidad clínica aparte?

SEOM–GEICAM–SOLTI clinical guidelines in advanced breast cancer (2022)



ESMO Metastatic Breast Cancer Living Guideline



García-Saenz JA et al. Clin Transl Oncol 2023. https://www.esmo.org/living-guidelines/

HER2-LOW como biomarcador

- ¿Es reproducible?
- ¿Es consistente?
- ¿Es una entidad biológica aparte?

Venetis K et al. Front Mol Biosc 2022

HER2-LOW como biomarcador

- **¿Es reproducible?**
- ¿Es consistente?
- ¿Es una entidad biológica aparte?

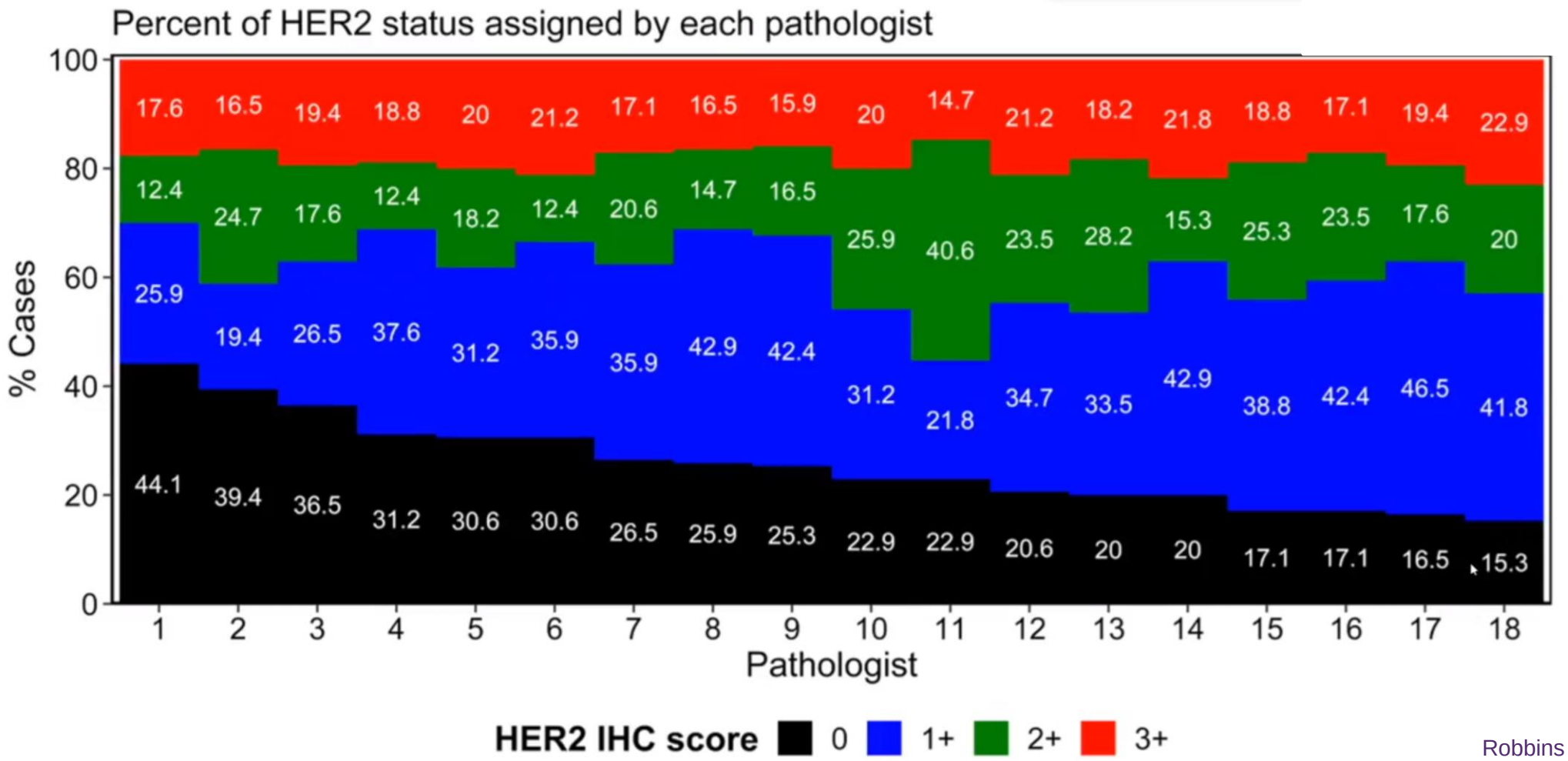
- Problemas preanalíticos (fijación FFPE, artefactos…)
- Problemas analíticos (heterogeneidad técnica)
- Variabilidad clínica (temporal, espacial…)

Venetis K et al. Front Mol Biosc 2022

HER2-LOW COMO BIOMARCADOR

¿Es consistente?

Multi-institutional Assessment of Pathologist Scoring HER2 Immunohistochemistry

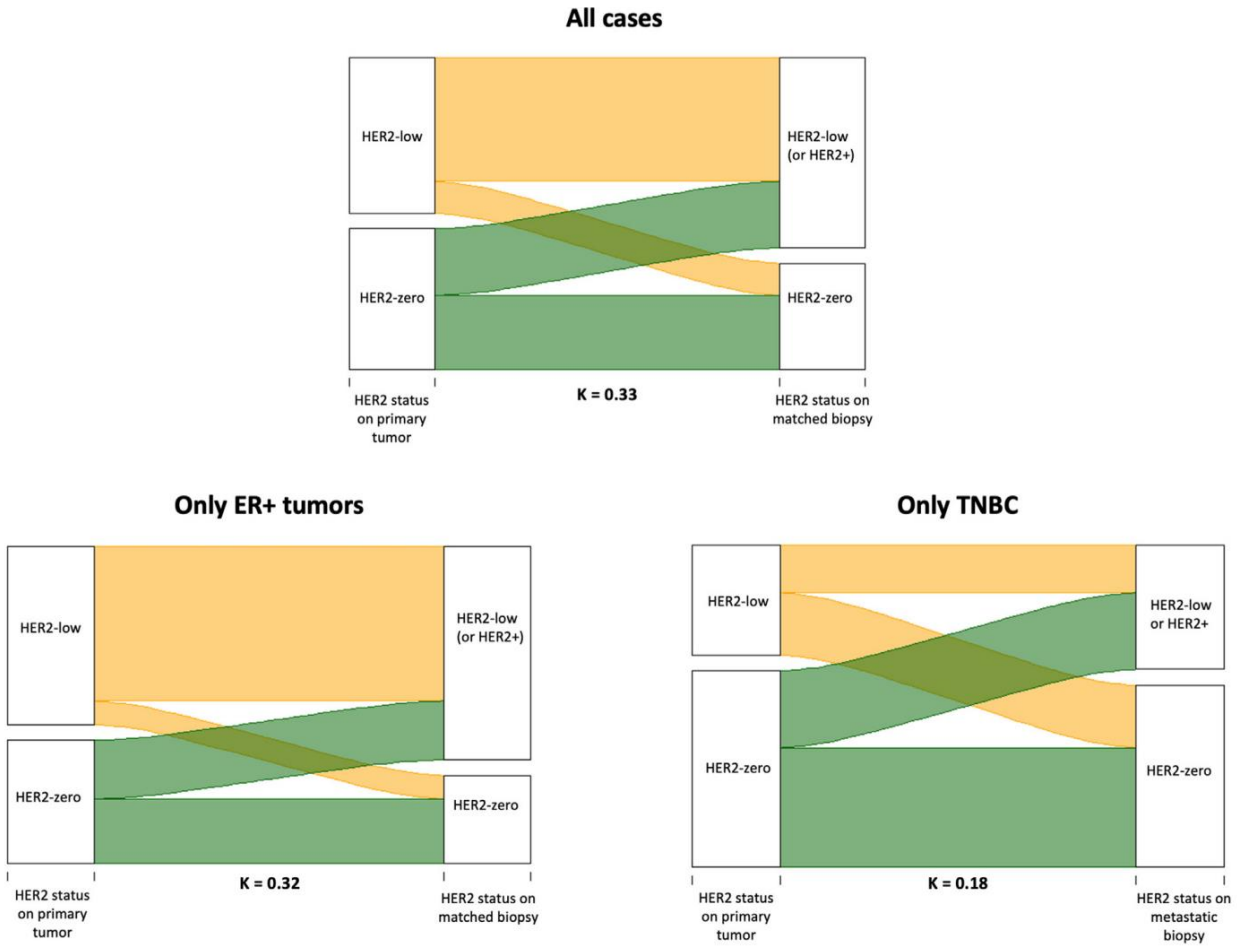


Robbins C et al. Mod Pathol 2023

HER2-LOW COMO BIOMARCADOR

¿Es consistente?

Evolution of low HER2 expression between early and advanced-stage breast cancer



- ↑ discordancias entre HER2 de biopsia de tumor primario y biopsia de metástasis. K=0,33
- 44% tumores HER2-0 en TP incrementaron su expresión de HER2 en la biopsia de la enfermedad avanzada
- 22% HER2-low en TP se convirtieron en HER2-0 en EA.

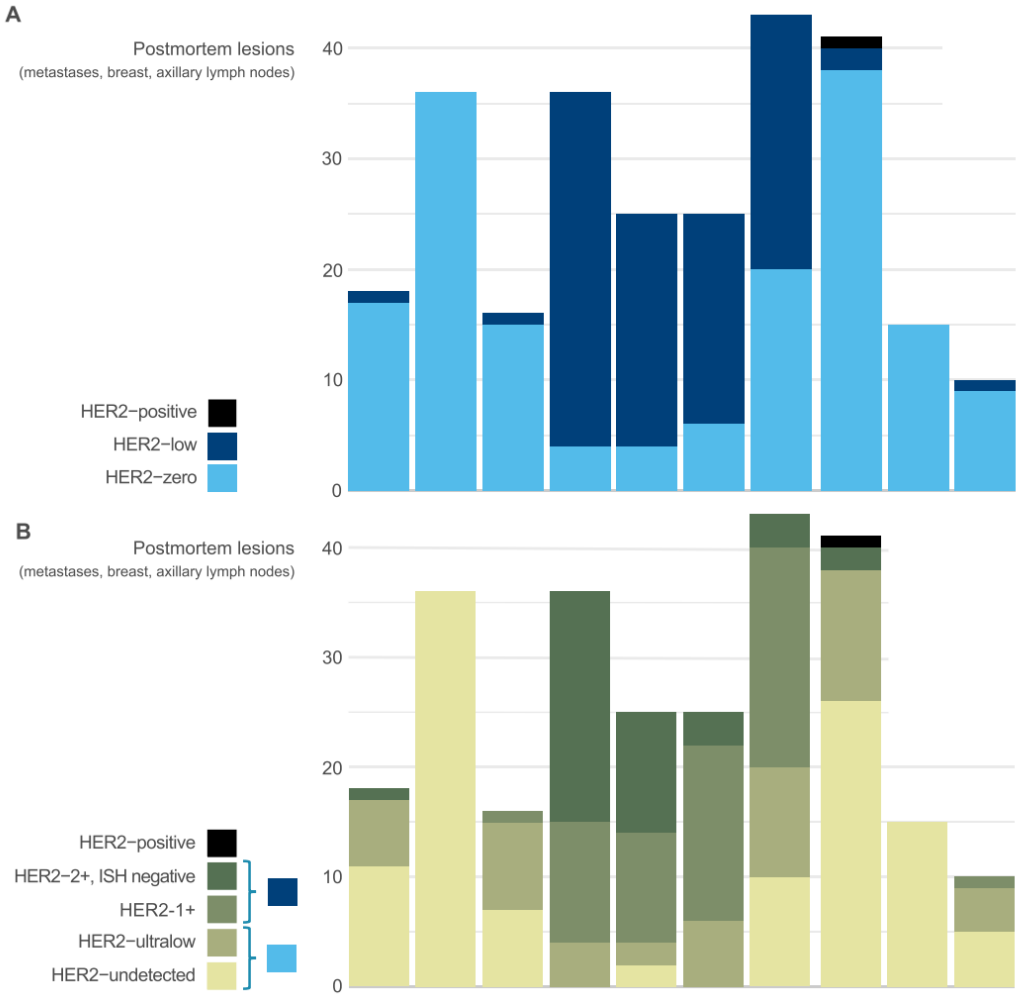
La expresión de HER2-low es dinámica y podría estar enriquecido en la enfermedad avanzada.
No valor pronóstico

Tarantino P et al. Eur J Cancer 2022

HER2-LOW COMO BIOMARCADOR

¿Es consistente?

Intra-patient and inter-metastasis heterogeneity of HER2-low status in metastatic breast cancer

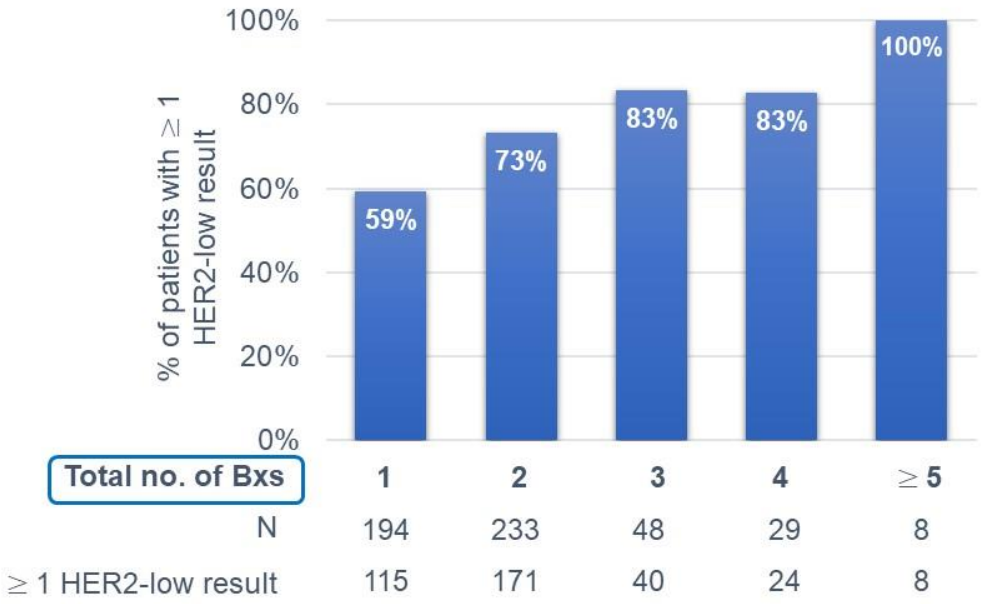


- 8/10 pacientes coexistían metástasis HER2-low y HER2-0
- 3/6 pacientes presentaban heterogeneidad intermetástasis a nivel hepático

↑ heterogeneidad intrapaciente inter-metástasis con respecto al HER2-low.

Geukens T et al. Eur J Cancer 2023

Results (Part 1) – Impact of Repeat Bxs:
Likelihood of HER2-low according to total number of Bxs



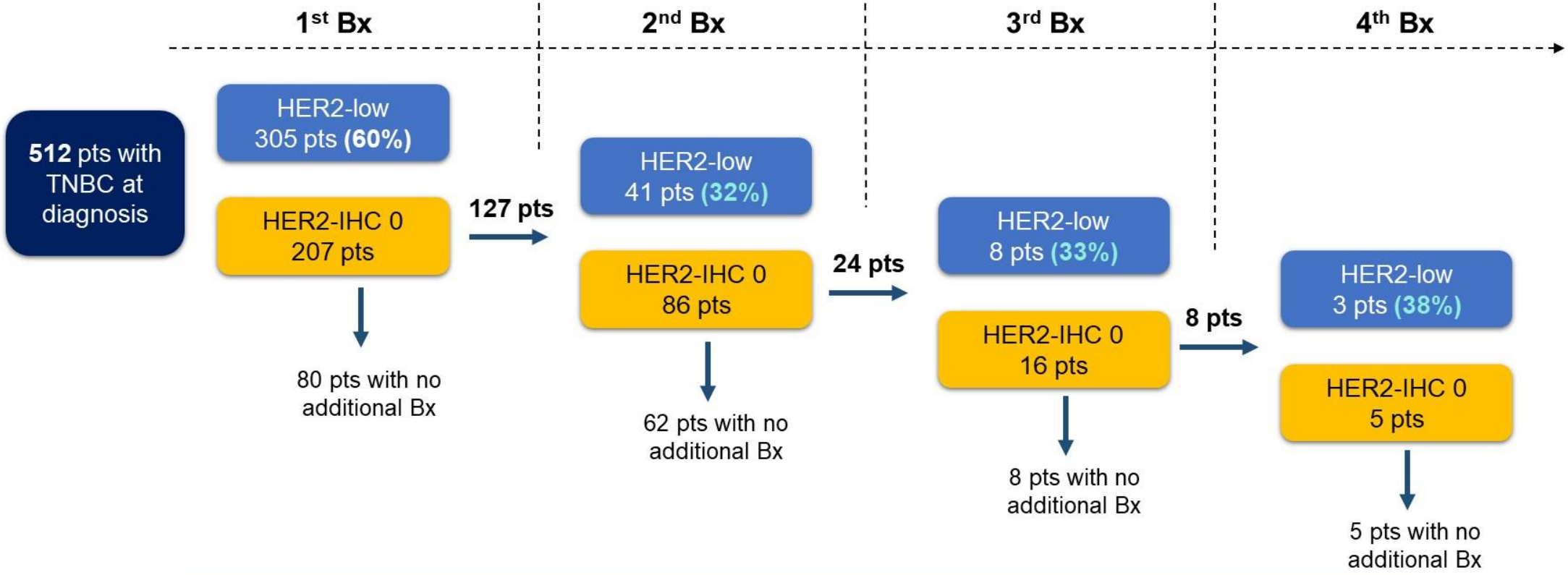
Total no. of Bxs	1	2	3	4	≥ 5
N	194	233	48	29	8
≥ 1 HER2-low result	115	171	40	24	8

The probability of a HER2-low result increases with the total number of Bxs

PRESENTED BY: Yael Bar, MD, PhD ybar@mgh.harvard.edu @BarYaelMD

Results (Part 1) – Impact of Repeat Bxs:

Detection of HER-low in successive serial Bxs for pts without a prior HER2-low result



With each successive Bx, a new HER2-low result was detected for 1/3 of patients with prior only HER2-IHC 0 results

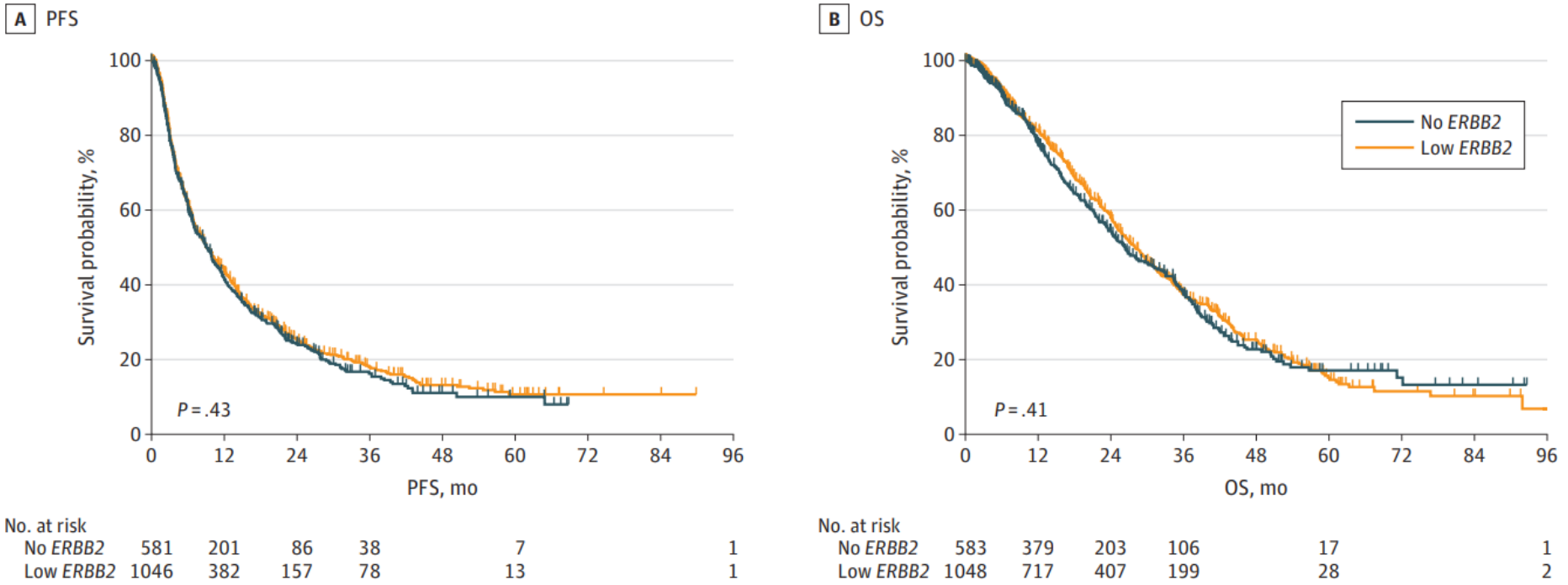
PRESENTED BY: Yael Bar, MD, PhD ybar@mgh.harvard.edu @BarYaelMD

HER2-LOW COMO BIOMARCADOR

¿Valor pronóstico?

En general la mayoría de estudios no objetivan un valor pronóstico.

Figure 2. Progression-Free Survival (PFS) and Overall Survival (OS) in Patients With Metastatic Breast Cancer With Hormone Receptor–Positive Low vs No *ERBB2* Expression Treated With Targeted Therapy in Combination With Endocrine Therapy



Mouabi J et al. JAMA Open Network 2023. Molinelli C et al. ASCO 2023

Prognostic value of HER2-low status in breast cancer: A systematic review and meta-analysis.

Setting	Population	OS HR (95%CI)	p value	DFS HR (95%CI)	p value	PFS HR (95%CI)	p value
Early	Overall	0.84 (0.77-0.92)	<0.001	0.86 (0.79-0.92)	<0.001		
	ER-positive	0.85 (0.78-0.93)	0.001	0.86 (0.80-0.93)	<0.001		
	ER-negative	0.87 (0.84-0.89)	<0.001	0.90 (0.78-1.04)	0.155		
Metastatic	Overall	0.94 (0.89-0.98)	0.008			0.99 (0.96-1.03)	0.710
	ER-positive	0.92 (0.87-0.98)	0.013			1.13 (0.94-1.35)	0.192
	ER-negative	0.91 (0.87-0.95)	<0.001			0.92 (0.84-1.02)	0.103

Asociación pronóstica, con un beneficio en SG entre las pacientes HER2-low frente a las HER2-0, tanto en la enfermedad localizada como avanzada.

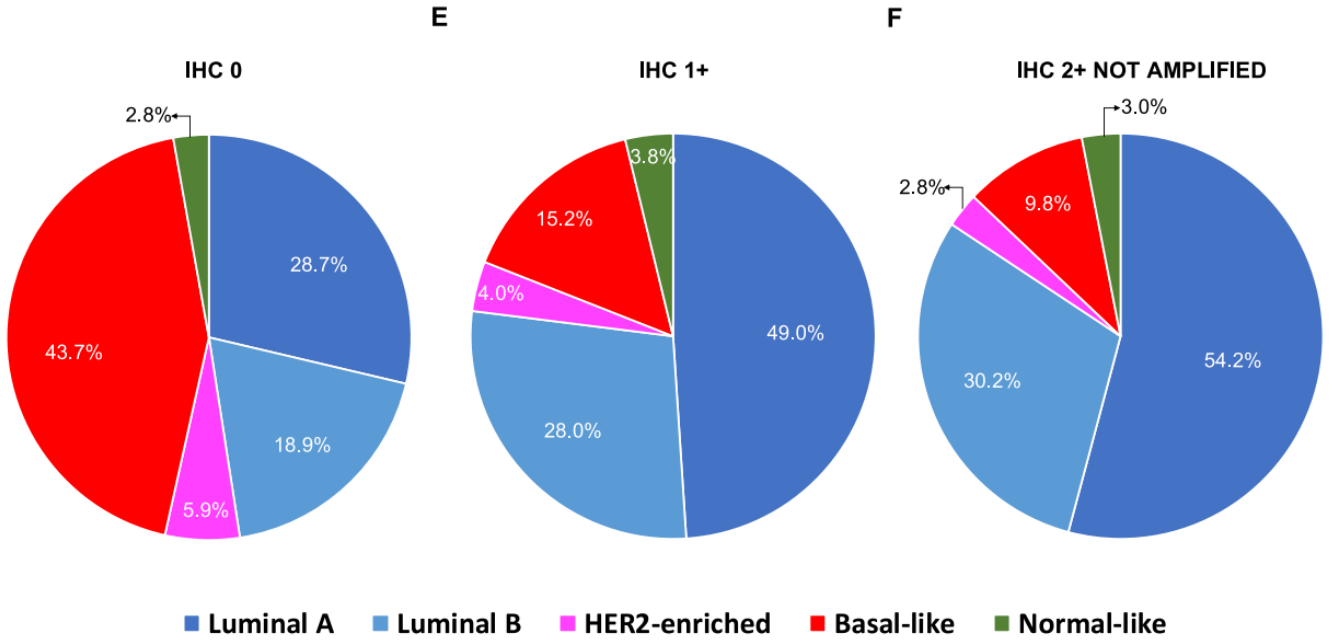
Mouabi J et al. JAMA Open Network 2023. Molinelli C et al. ASCO 2023

HER2-LOW COMO BIOMARCADOR

¿Se trata de un subgrupo molecular aparte?

QUESTION 2: Is HER2-low a distinct molecular entity, with a different biology compared with HER2-0 tumors?

STATEMENT: No substantial molecular differences have been demonstrated between HER2-low and HER2-0 tumors, after correcting for the expression of hormone receptors. Consequently, HER2-low should not be considered a distinct molecular entity, but rather a heterogeneous group of tumors, with biology primarily driven by the presence or absence of hormone receptor expression. [II, A]



- Subgrupo heterogéneo a nivel molecular.
- Determinante principal del perfil de expresión génica es la expresión de RH:
  - RH+ → luminal A o B
  - RH- → basal-like
- Diferencias mínimas en la expresión génica entre HER2-low y HER2-0

Tarantino P et al. Ann Oncol 2023. Schettini F et al. NPJ Breast Cancer 2023

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

American Society of Clinical Oncology–College of American Pathologists Guideline Update

Recommendations

The 2018 ASCO–College of American Pathologists (CAP) recommendations for HER2 testing are affirmed.

Wolff A et al. Arch Pathol Lab Med 2023

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

American Society of Clinical Oncology–College of American Pathologists Guideline Update

Recommendations

The 2018 ASCO–College of American Pathologists (CAP) recommendations for HER2 testing are affirmed.

No se recomienda el uso del término HER2-low

- Se recomienda mantener la denominación de HER2-negativo para aquellos tumores HER2 0, 1 y 2+ sin amplificación.
- Añadir a continuación el score IHQ semicuantitativo.
- Recomendaciones especiales para distinguir 1+ de 0.

Wolff A et al. Arch Pathol Lab Med 2023

ESMO Expert Consensus Statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer

Description of staining	Denomination by 2018 ASCO/CAP guidelines	Conclusion by 2018 ASCO/CAP guidelines	Conclusion by 2023 ESMO clinical practice recommendations	
- No staining	HER2-0	HER2-negative	**HER2-0**	*HER2-null **
- Incomplete or faint staining in ≤10% of invasive tumor cells	HER2-0	HER2-negative		*HER2-ultralow (or >0 <1+) **
- Incomplete or faint staining in > 10% of invasive tumor cells	HER2 1+	HER2-negative	**HER2-low**	
- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-negative)	HER2 2+ non amplified	HER2-negative	**HER2-low**	
- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-positive)	HER2 2+ amplified	HER2-positive	**HER2-positive**	
- Intense complete membrane staining in > 10% of invasive tumor cells	HER2 3+	HER2-positive	**HER2-positive**	

Tarantino P et al. Ann Oncol 2023

ESMO Expert Consensus Statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer

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- Incomplete or faint staining in ≤10% of invasive tumor cells	HER2-0	HER2-negative		*HER2-ultralow (or >0 <1+) **
- Incomplete or faint staining in > 10% of invasive tumor cells	HER2 1+	HER2-negative	**HER2-low**	
- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-negative)	HER2 2+ non amplified	HER2-negative	**HER2-low**	
- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-positive)	HER2 2+ amplified	HER2-positive	**HER2-positive**	
- Intense complete membrane staining in > 10% of invasive tumor cells	HER2 3+	HER2-positive	**HER2-positive**	

Se mantiene la definición de HER2-negativo.

Tarantino P et al. Ann Oncol 2023

ESMO Expert Consensus Statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer

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- Incomplete or faint staining in > 10% of invasive tumor cells	HER2 1+	HER2-negative	**HER2-low**	
- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-negative)	HER2 2+ non amplified	HER2-negative	**HER2-low**	
- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-positive)	HER2 2+ amplified	HER2-positive	**HER2-positive**	
- Intense complete membrane staining in > 10% of invasive tumor cells	HER2 3+	HER2-positive	**HER2-positive**	

Se mantiene la definición de HER2-negativo.

Sí se considera adoptar las nuevas definiciones de:

- HER2-low
- HER2-ultralow
- HER2-null

Condicionadas a los resultados del estudio DB06

Tarantino P et al. Ann Oncol 2023

ESMO Expert Consensus Statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer

Description of staining	Denomination by 2018 ASCO/CAP guidelines	Conclusion by 2018 ASCO/CAP guidelines	Conclusion by 2023 ESMO clinical practice recommendations	
- No staining	HER2-0	HER2-negative	**HER2-0**	*HER2-null **
- Incomplete or faint staining in ≤10% of invasive tumor cells	HER2-0	HER2-negative		*HER2-ultralow (or >0 <1+) **
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- Weak to moderate complete membrane staining in > 10% of invasive tumor cells (ISH-positive)	HER2 2+ amplified	HER2-positive	**HER2-positive**	
- Intense complete membrane staining in > 10% of invasive tumor cells	HER2 3+	HER2-positive	**HER2-positive**	

Se mantiene la definición de HER2-negativo.

Sí se considera adoptar las nuevas definiciones de:

- HER2-low
- HER2-ultralow
- HER2-null

Condicionadas a los resultados del estudio DB06

- Se recomienda documentar el score IHQ.
- No incluir estas definiciones en el informe AP (interpretación clínica).

Tarantino P et al. Ann Oncol 2023

HER2-LOW COMO BIOMARCADOR

¿Realmente es un biomarcador?

- Biomarcador creado por los criterios de inclusión del estudio DESTINYBreast04:
  - Excluidos pacientes con HER2-0

- Sin diferencias entre IHQ 1+ y 2+ en DESTINY Breast 04
  - mPFS 10,3 m en IHQ 1+ y 10,1 meses en IHQ 2+ y FISH negativo.

Modi S et al. NEJM 2022

DAISY (NCT04132960): Study design

- Metastatic breast cancer patients
- ≥18 years old
- ≥1 chemotherapy regimen in metastatic setting

HER2 status* of metastatic baseline biopsy determines the final cohort

COHORT 1
N=74
HER2 IHC3+ or IHC2+/ISH+
Resistant to taxanes, trastuzumab and TDM-1

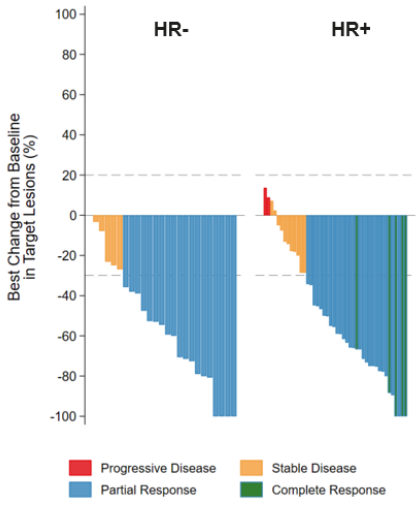
COHORT 2
N=44
HER2 IHC2+ or IHC2+/ISH-
Resistant to anthracyclines and taxanes.
If HR+, also resistant to CDK4/6 inhibitors and HT

COHORT 3
N=44
HER2 IHC0+
Resistant to anthracyclines and taxanes.
If HR+, also resistant to CDK4/6 inhibitors and HT

Pacientes politratados (mediana de líneas previas 5)

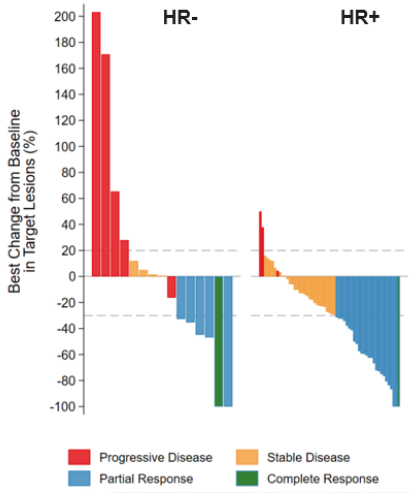
Best Objective Response

HER2-positivo



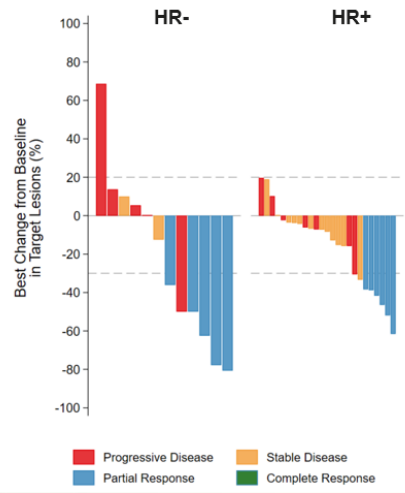
BOR 70,6%
mPFS 11,1 m

HER2-"low"



BOR 37,5%
mPFS 6,7 m

HER2 0



BOR 29,7%
mPFS 4,2 m

Diéras V et al. SABCS 2022

HER2-LOW COMO BIOMARCADOR

¿Hasta cuándo?

- DESTINYBreast06:
  - HER2 1+ y HER2 2+ sin amplificación (“HER2-low”)
  - HER2 >0 y < 1+ (“HER2-ultralow”)
  - No incluye HER2-0 (“HER2-null”)

The American Society of Clinical Oncology–College of American Pathologists Guideline Update for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

How Low Can HER2 Go?

Stuart J. Schnitt, MD; Paolo Tarantino, MD; Laura C. Collins, MD

protein expression at all (considered by some as HER2 "null").[12] Nevertheless, if clinical trials ultimately demonstrate that patients with HER2 0 tumors have a response rate to ADCs similar to that seen in HER2-low tumors, the attempt to distinguish HER2 1+ from HER2 0 cases may become clinically irrelevant, and the current efforts to make this distinction will have been a tempest in a teapot.

CONCLUSIONES

- Se consolida el papel de trastuzumab deruxtecan en el algoritmo terapéutico del CM HER2-positivo.
    - La importancia actual de evaluar el SNC para la toma de decisiones.
    - Datos sólidos con tucatinib-capecitabina-trastuzumab
    - Datos esperanzadores con trastuzumab deruxtecan
- HER2-low como biomarcador:
    - Indiscutible beneficio de trastuzumab deruxtecan en estas pacientes.
    - ↓ reproducible, ↓ consistente, biomarcador artificial