Il carcinoma mammario metastatico HER2-positivo: novità e cambiamenti nel paradigma terapeutico

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DISCLOSURES

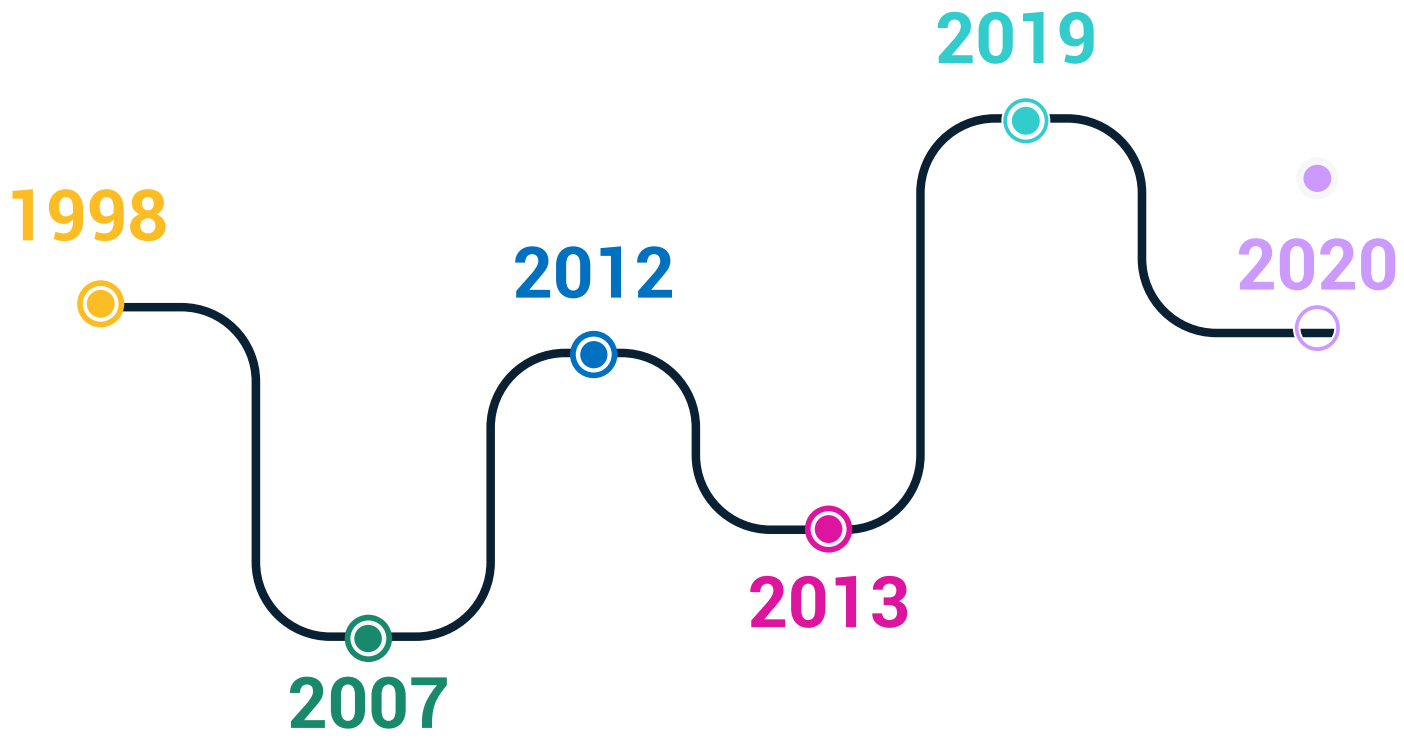
Advisory board membership: AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Exact Sciences, Gilead, Merck Serono, MSD, Novartis, Pfizer, Olema Oncology, Pierre Fabre

Invited speaker: AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK Novartis, Zentiva

Expert testimony: Eli Lilly

The evolving scenario of HER2+ MBC

FDA approval timeline



Trastuzumab + CT

Lapatinib + capecitabine

Trastuzumab + Pertuzumab + CT

TDM1

T-DXD

Tucatinib

REVIEW

Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival

ESMO OPEN CANCER HORIZONS
doi: 10.1016/j.esmoop.2022.100409

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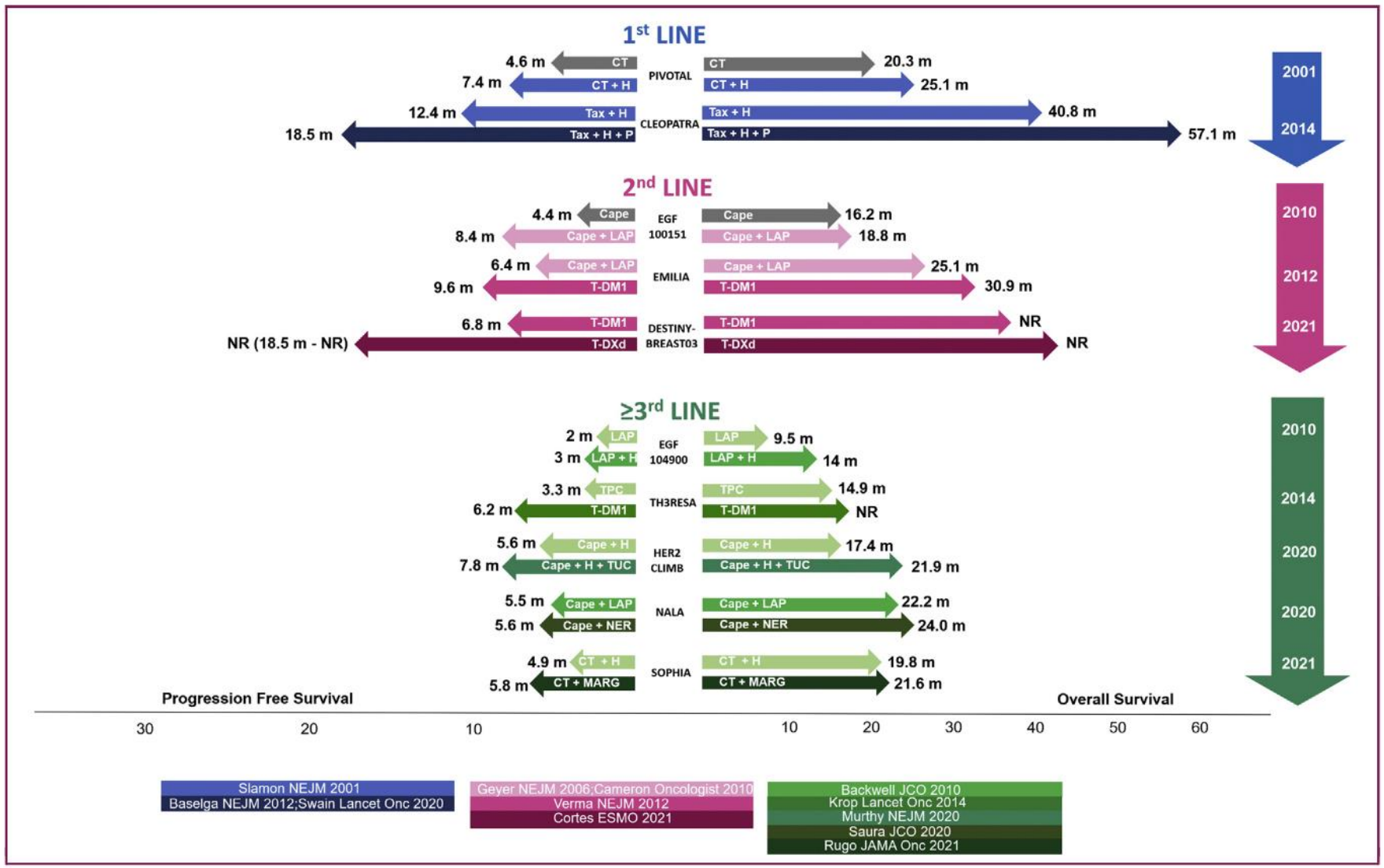
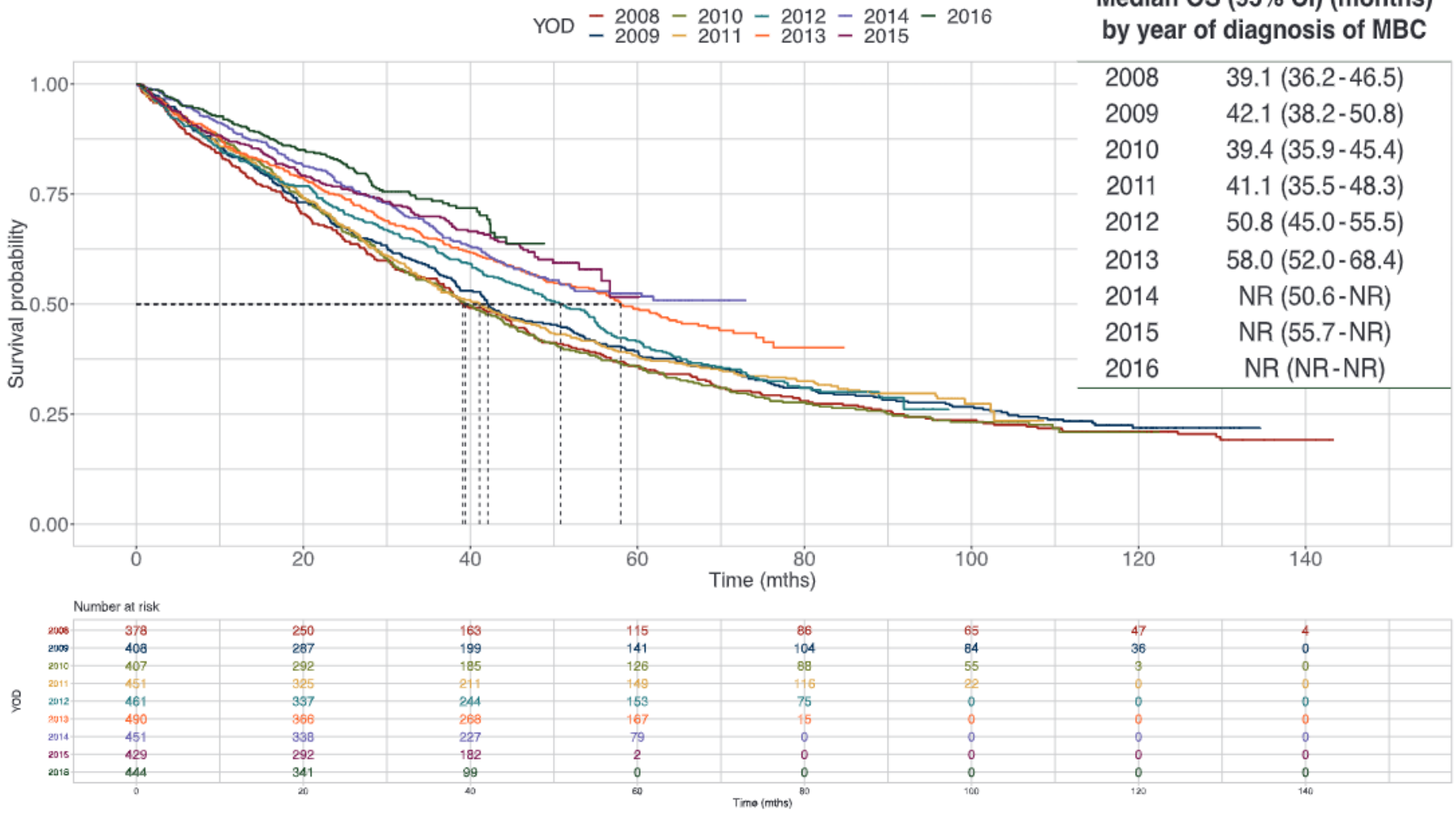


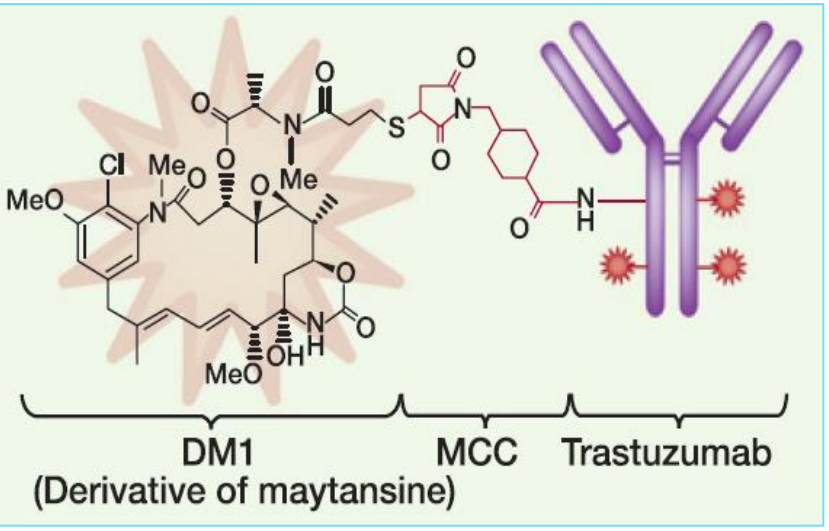
Real-world OS of HER2+ MBC over time



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

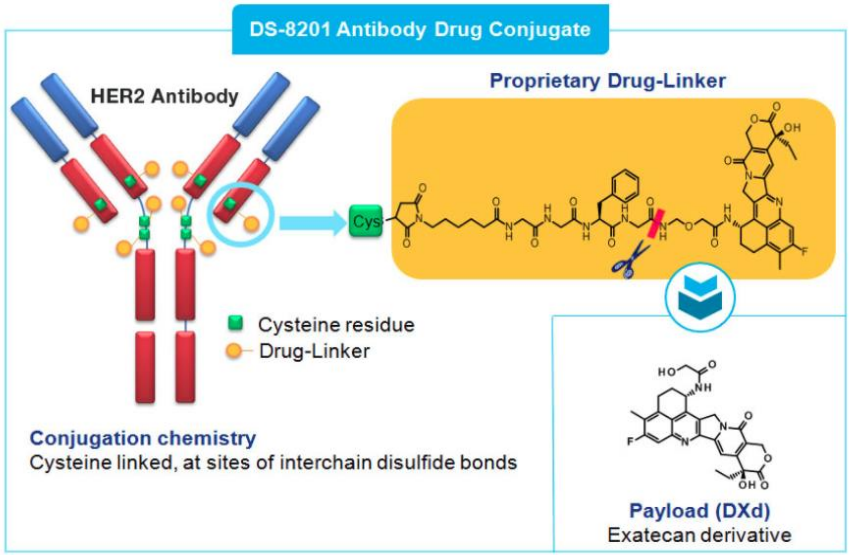
Grinda T et al, ESMO Open 2021

Anti-HER2 ADCs



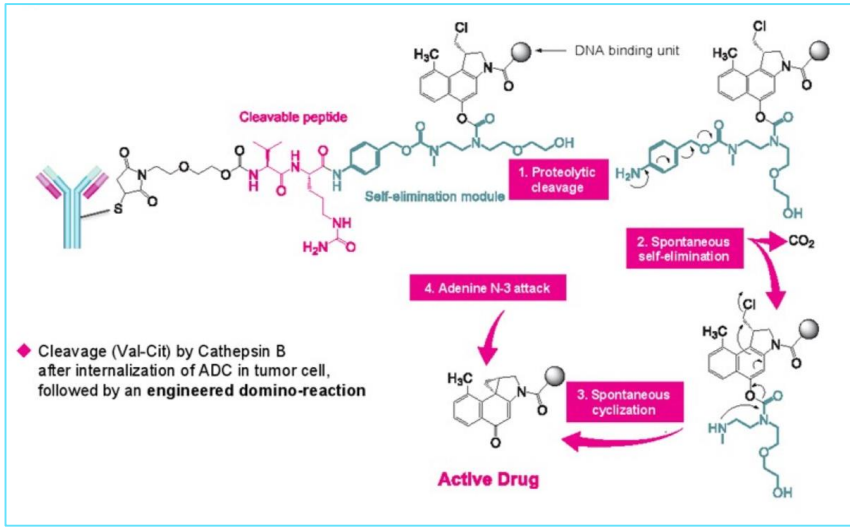
T-DM1

Payload: maytansine derivative
Drug/antibody ratio: 3.5
Linker: not cleavable
Bystander activity: minimal



DS-8201

Payload: topoisomerase I inh
Drug/antibody ratio: 7.7
Linker: cleavable
Bystander activity: yes
(membrane-soluble payload)



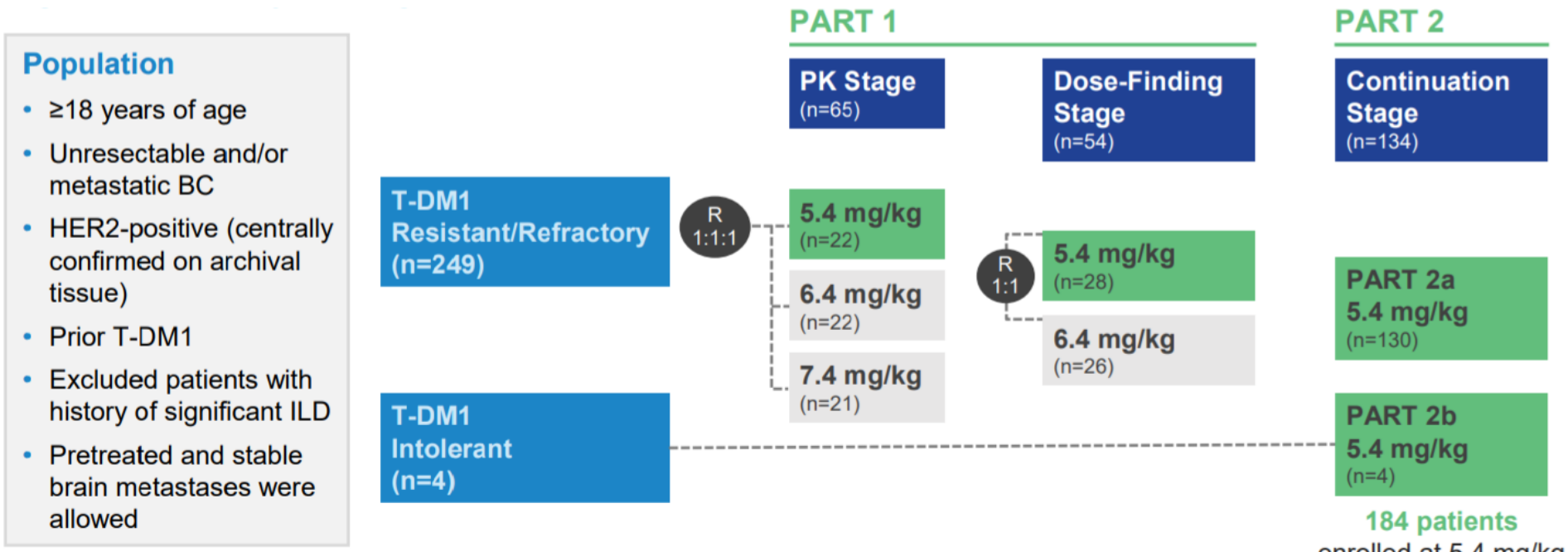
SYD985

Payload: duocarmycin analogue
Drug/antibody ratio: 2.8
Linker: cleavable
Bystander activity: yes
(extracellular cleavage)

Trail et al, Pharmacology and Therapeutics 2018

T-DM1 refractory-resistant setting

DESTINY-Breast01 phase II trial



BC, breast cancer; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; PK, pharmacokinetics; T-DM1, trastuzumab emtansine.

100% received prior trastuzumab and TDM1, 65.8% prior pertuzumab, 54.3% other prior anti-HER2 tx; **35.9% best response to TDM1=PD**

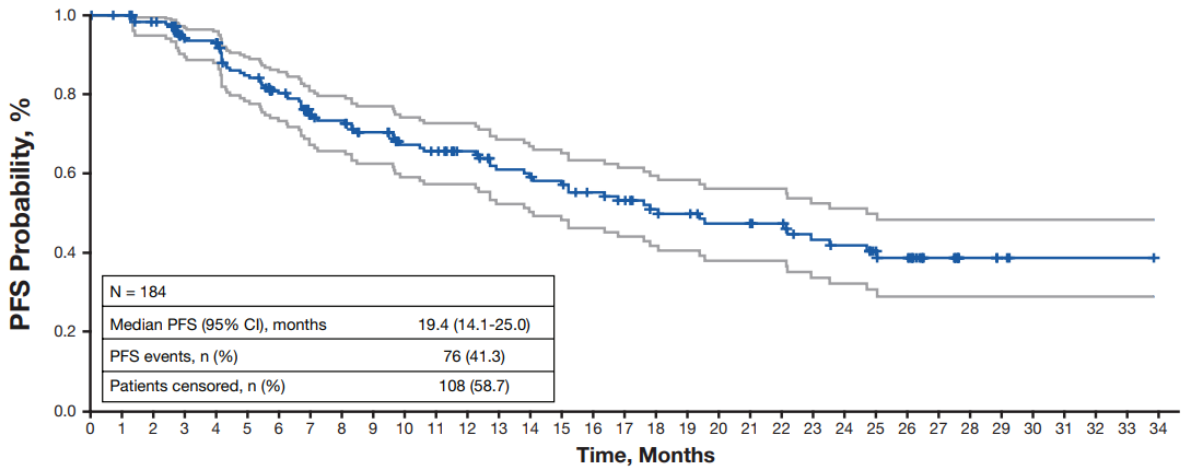
Modi et al, SABCS 2020; Modi et al, NEJM 2020

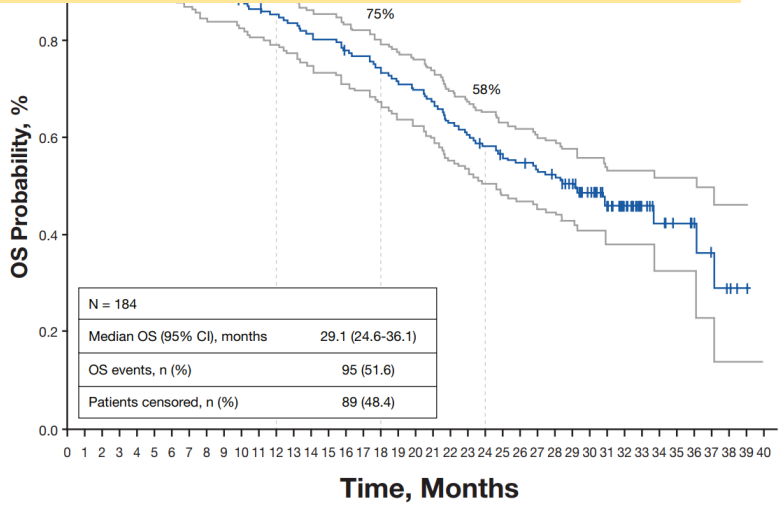
T-DM1 refractory-resistant setting

DESTINY-Breast01 phase II trial

Confirmed ORR by ICR, n (%) 95% CI	114 (62.0) 54.5-69.0
CR	13 (7.1)
PR	101 (54.9)
SD	65 (35.3)
PD	3 (1.6)

FDA accelerated approval in Dec. 2019
EMA conditional marketing authorization in Dec. 2020



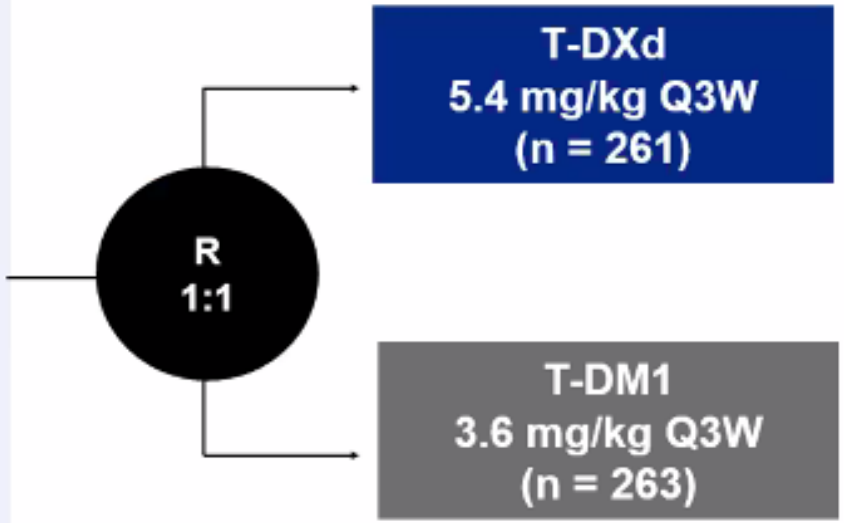


Modi et al, SABCS 2020; Modi et al, NEJM 2020; Saura et al, ESMO 2021

DESTINY-Breast03: study design

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Cortes J, ESMO 2021, N Engl J Med 2022

DESTINY-Breast03: patients characteristics

	T-DXd (n = 261)	T-DM1 (n = 263)
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, %	99.6	99.6
Region, %		
Europe	20.7	19.0
Asia	57.1	60.8
North America	6.5	6.5
Rest of world	15.7	13.7
HER2 status (IHC[a], %)		
3+	89.7	88.2
2+ (ISH amplified)	9.6	11.4
1+ | Not Evaluable | Not Examined	0.4 | 0.4 | 0	0 | 0.4 | 0
ECOG PS, %		
0 | 1 | Missing	59.0 | 40.6 | 0.4	66.5 | 33.1 | 0.4
Hormone receptor, %		
Positive | Negative	50.2 | 49.8	51.0 | 49.0
Brain metastases, %		
Yes | No	23.8 | 76.2	19.8 | 80.2
Visceral disease, %		
Yes | No	70.5 | 29.5	70.3 | 29.7

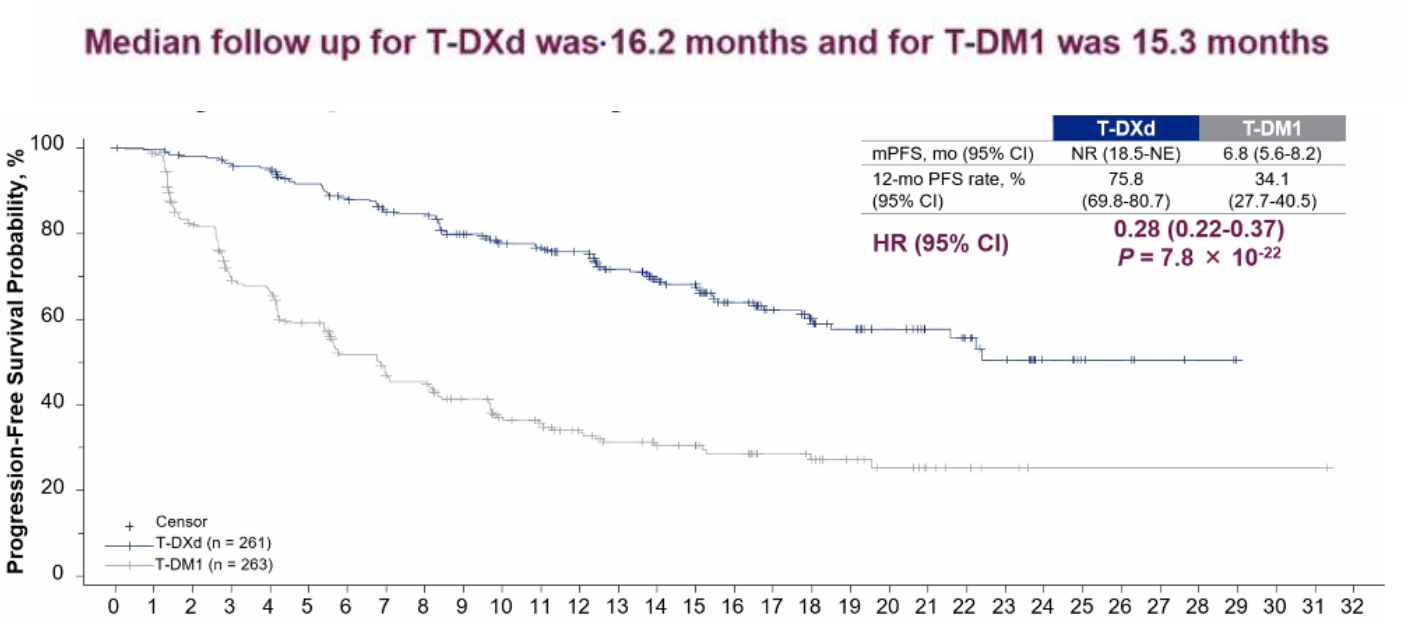
Cortes J, ESMO 2021, N Engl J Med 2022

DESTINY-Breast03: prior treatments

	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)[a], n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy[b], %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

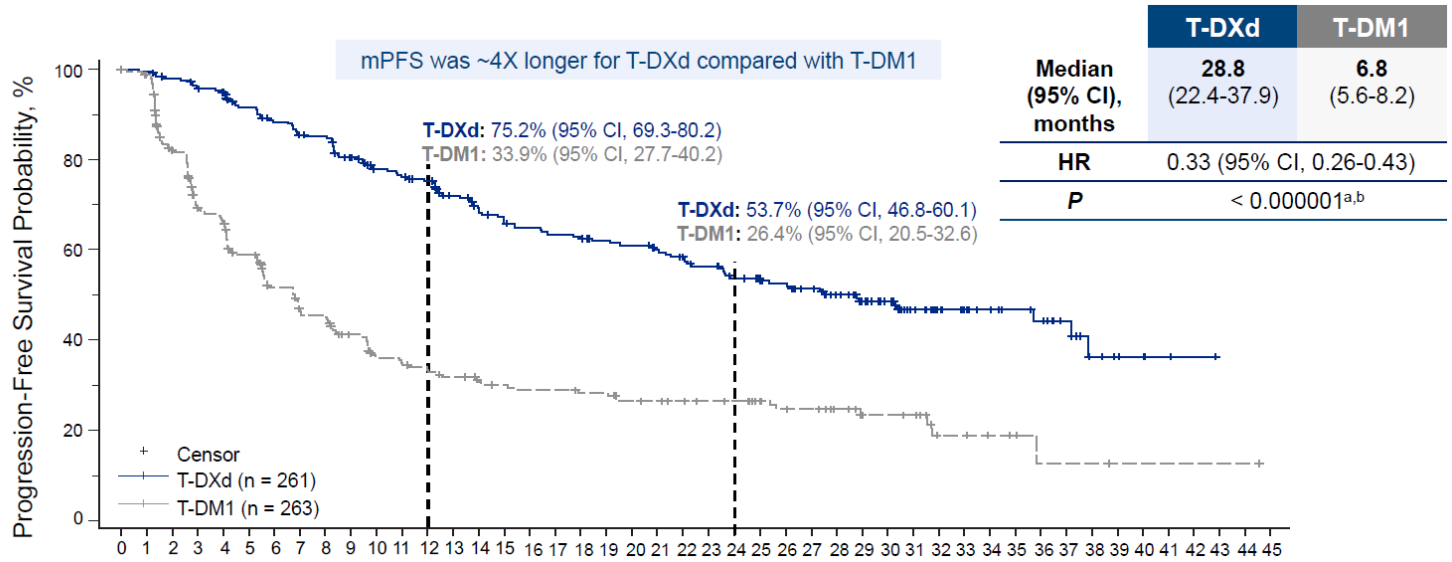
Cortes J, ESMO 2021, N Engl J Med 2022

DESTINY-Breast03: primary endpoint results (PFS by BICR)



PFS by Investigator assessment: median 25 months vs 7.2, HR 0.27

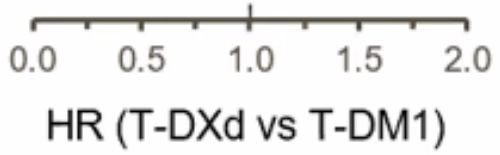
Updated PFS analysis (BICR)



Cortes ESMO 2021, J, N Engl J Med 2022; Hurvitz et al, SABCS 2022, The Lancet Oncol 2023

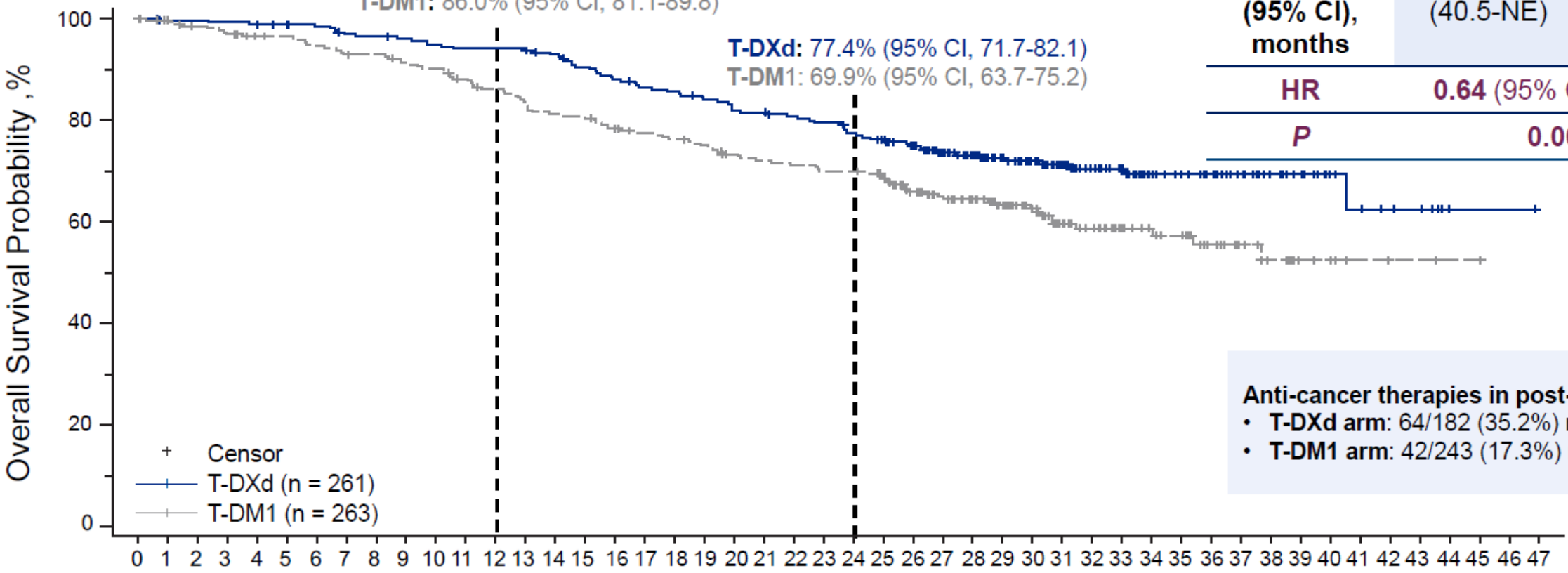
DESTINY-Breast03: PFS in subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)



Cortes J, N Engl J Med 2022

DESTINY-Breast03: Overall Survival



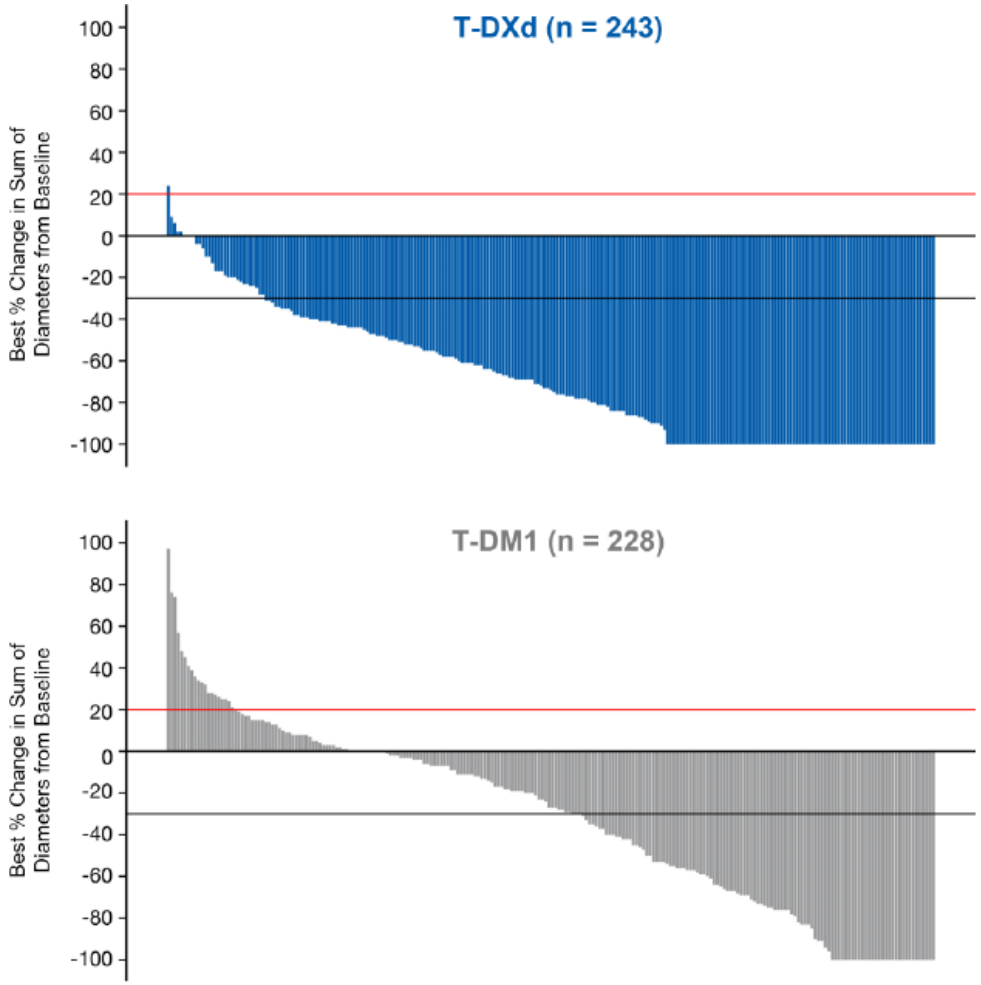
	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Anti-cancer therapies in post-trial setting:

- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Cortes J, N Engl J Med 2022; Hurvitz et al, SABCS 2022, The Lancet Oncol 2023

DESTINY-Breast03: ORR and Best response



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

Cortes J, N Engl J Med 2022; Hurvitz et al, SABCS 2022, The Lancet Oncol 2023

Overall safety summary

n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE	252 (98.1)	226 (86.6)
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious drug-related TEAE	28 (10.9)	16 (6.1)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with an outcome of death	0 (0.0)	0 (0.0)

- **Median treatment duration was 14.3 months (range, 0.7-29.8) for T-DXd and 6.9 months (range, 0.7-25.1) for T-DM1**
- The most common TEAE associated with treatment discontinuation for T-DXd was ILD/pneumonitis[a] (8.2%) and for T-DM1 was thrombocytopenia[b] (2.7%)
- The most common TEAEs associated with dose reduction for T-DXd were nausea (6.2%) and neutropenia[c] (3.5%) and for T-DM1 were thrombocytopenia[b] (4.2%) and ALT and AST increased (2.7% each)

[a]Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or T-DM1 (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). [b]This category includes the preferred terms platelet count decreased and thrombocytopenia. [c]This category includes the preferred terms neutrophil count decreased and neutropenia.

Cortes J, ESMO 2021, N Engl J Med 2022

Destiny03: Adverse Events of Special Interest Interstitial Lung Disease and Cardiac

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

LVEF, left-ventricular ejection fraction.
[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.

Cortes, et al ESMO 2021

Beware of the toxicities: learn to know ILD

Incidence of ILD over time: pooled analysis of 8 single arm phase 1 and 2 T-DXd monotherapy studies

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

In Dec 2019 toxicity management guidelines were updated

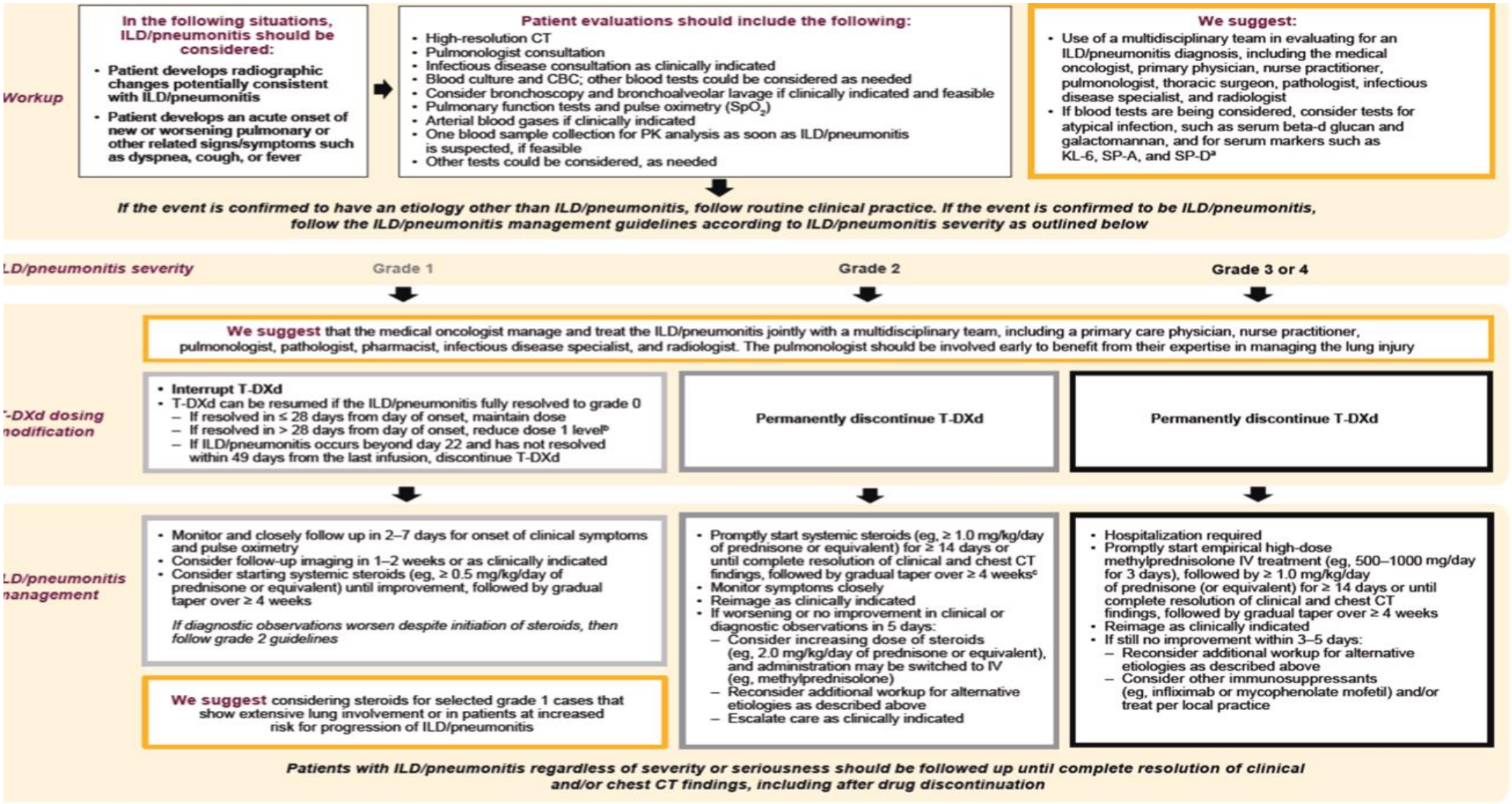
Most ILD events were low grade (78% of pts with ILD had G1/2 events) and occurred in the first 12 mo of tx, with lowered risk for pts on tx > 12 mo.

The adjudication committee identified ILD earlier than investigators in 48% of cases suggesting opportunity for early detection and intervention.

Close monitoring, prompt recognition, and proactive management of ILD using current management guidelines may help to improve ILD outcomes.

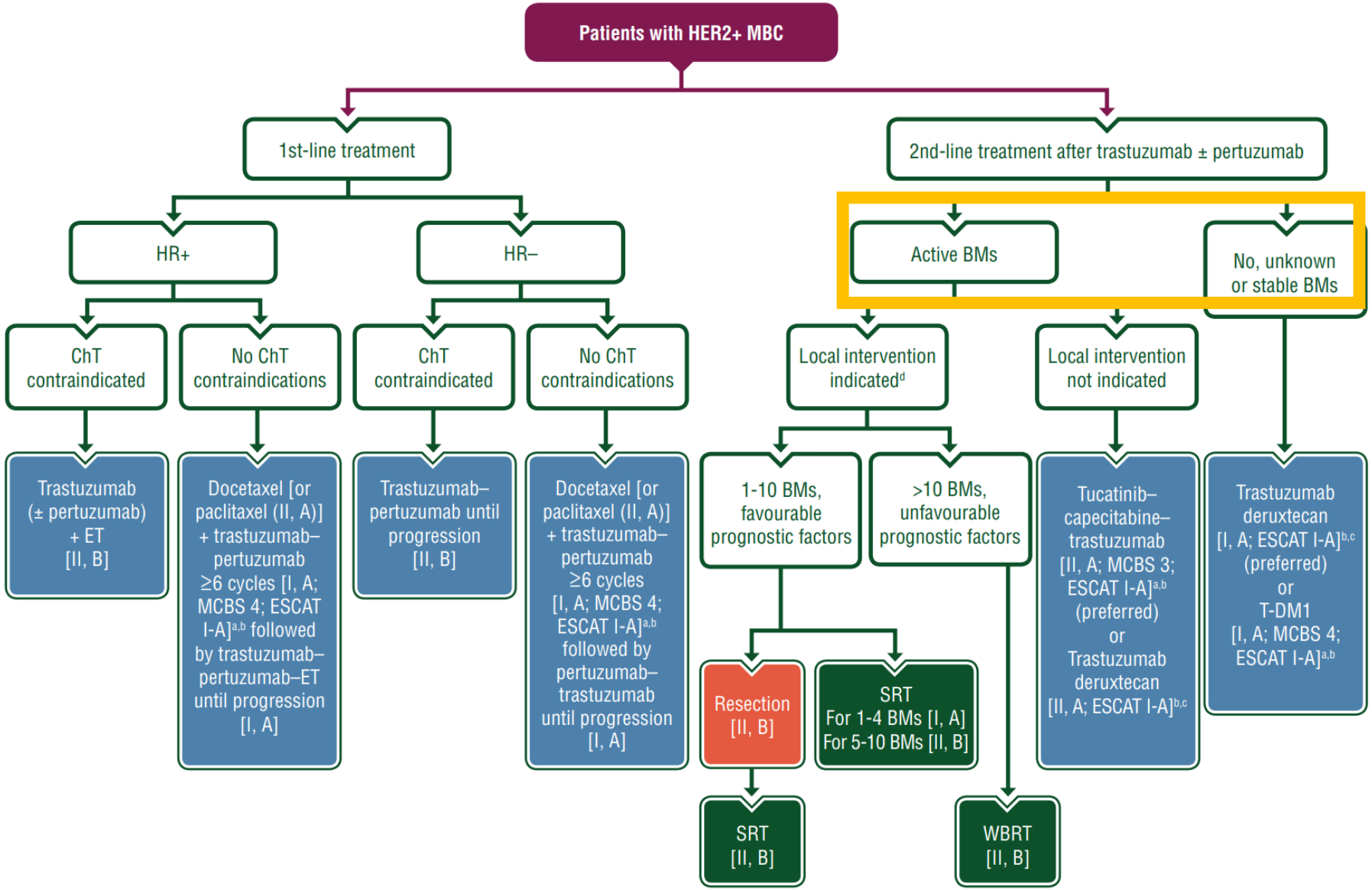
Powell et al, AACR 2021; Modi ESMO Congress 2021

Algorithm for ILD diagnosis and management



Swain et al *Cancer Treat Reviews* 2022;106

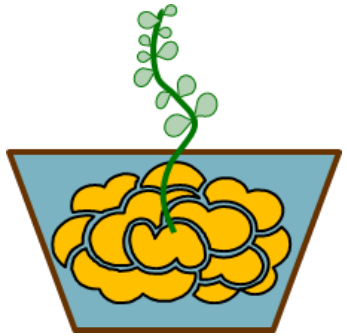
New treatment algorithm for HER2+ ABC



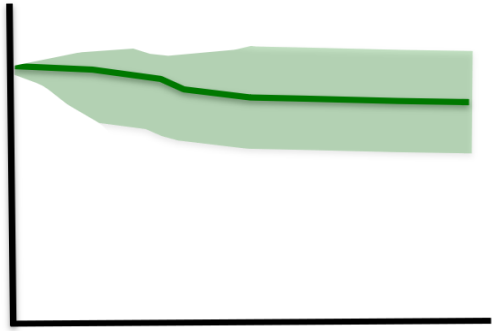
Stratification according to BMs (and BM activity)

Modified from Gennari et al, Ann Oncol 2021; ESMO guidelines

Brain Metastases are frequent in Stage IV HER2+ mBC



Inherent neuro-tropism of HER2+ BC
(increased brain parenchymal colonization of metastatic HER2+ BC cells)



Prolonged survival and better extra-CNS disease control with contemporary regimens for eBC and mBC

CNS as a sanctuary site for metastases in eBC
(inadequate drug penetration of anti-HER2 agents into the brain parenchyma through the BBB)

TUCATINIB for active BCBM

HER2CLIMB

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
- No evidence of brain metastases

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

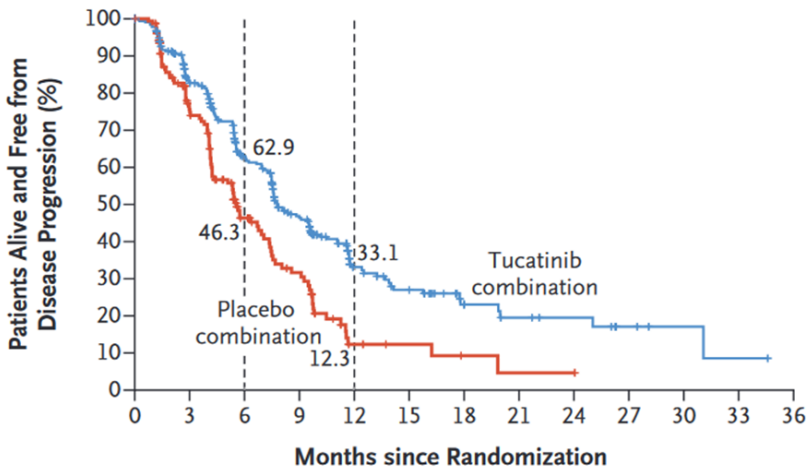
Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

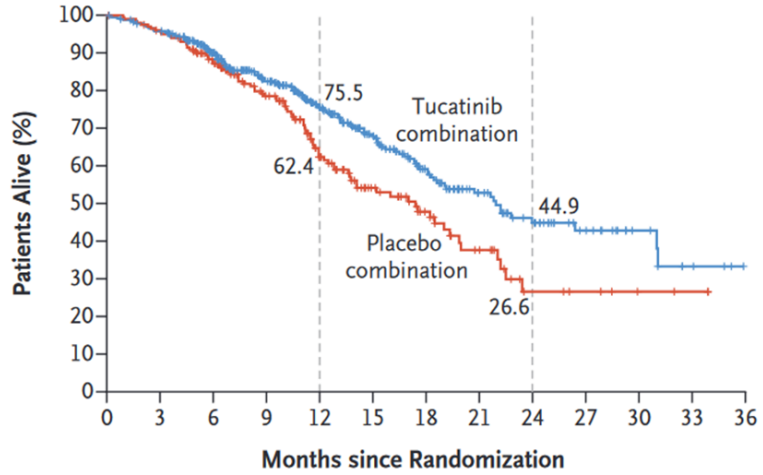
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

HR+ ~60%; median previous lines of Tx: 4; 100% received trast, pert and T-DM1



	Events/pts	mPFS	HR (95%CI
Tucatinib combination	178/320	7.8	
Placebo combination	97/160	5.6	0.54 (0.42-0.71)

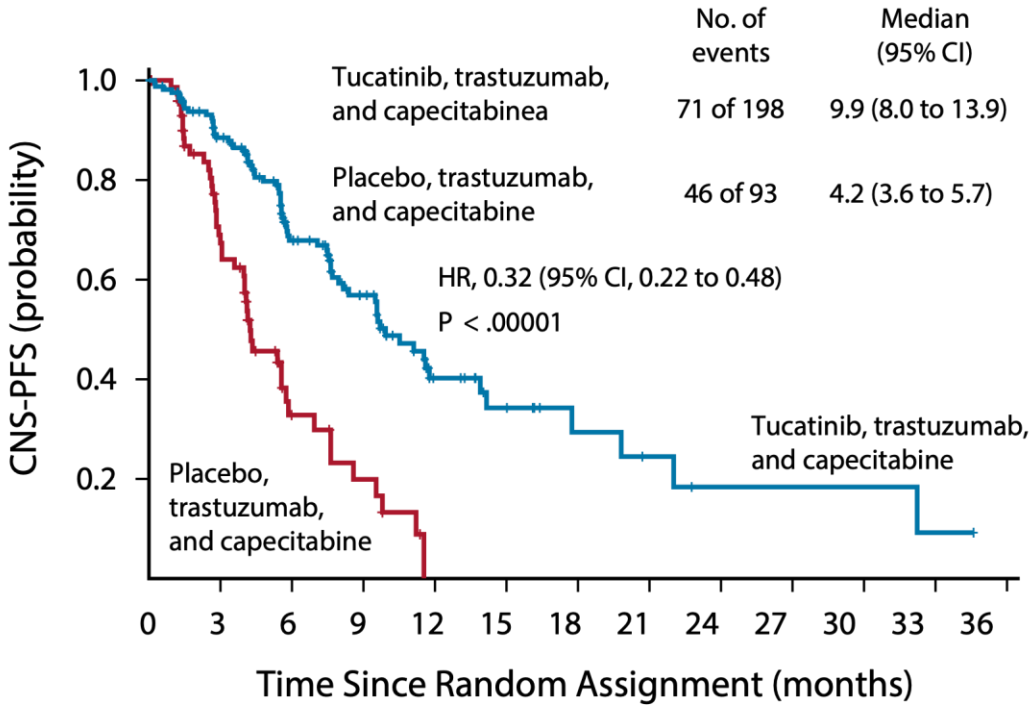


	Events/pts	mOS	HR (95%CI
Tucatinib combination	130/410	21.9	
Placebo combination	85/202	17.4	0.66 (0.50-0.88)

Murthy RK, et al. N Engl J Med 2020

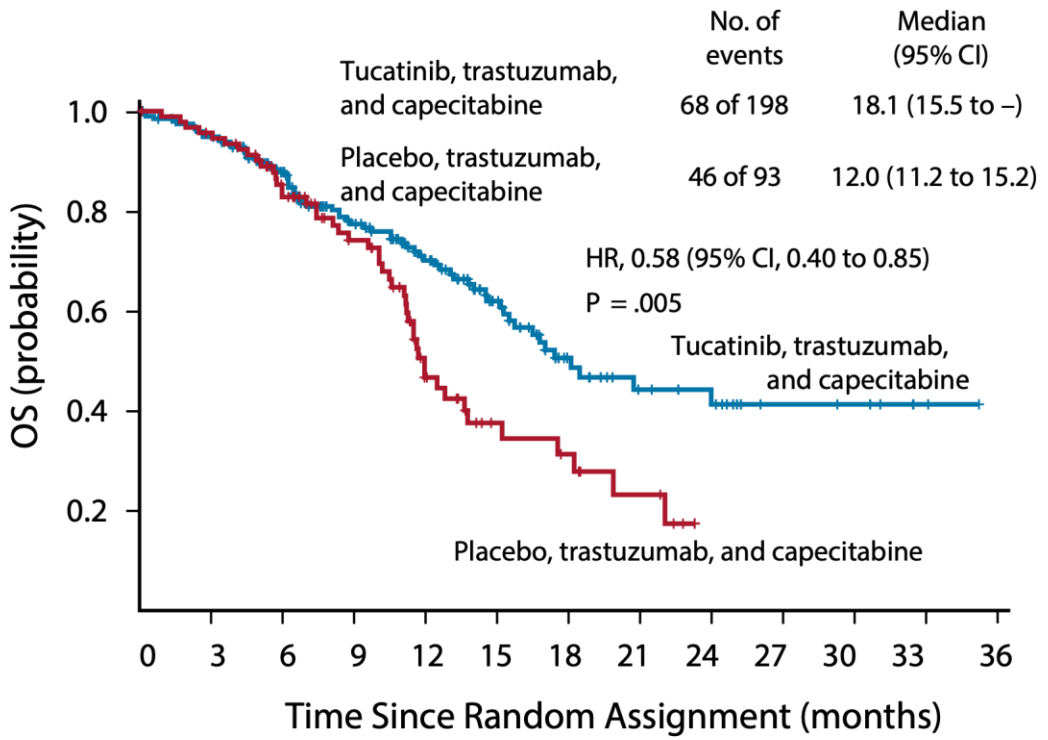
TUCATINIB for active BCBM

HER2CLIMB: patients with CNS involvement



No. at risk:

Tucatinib, trastuzumab, and capecitabine	198	132	74	45	18	11	6	4	2	2	2	1	0
Placebo, trastuzumab, and capecitabine	93	41	11	6	0	0	0	0	0	0	0	0	0



No. at risk:

Tucatinib, trastuzumab, and capecitabine	198	184	146	108	79	49	26	17	14	7	6	2	0
Placebo, trastuzumab, and capecitabine	93	87	67	49	23	12	9	5	0	0	0	0	0

Curigliano G, Mueller V, Borges V, et al. *Ann Oncol*, 2022; doi:10.1016/j.annonc.2021.12.005

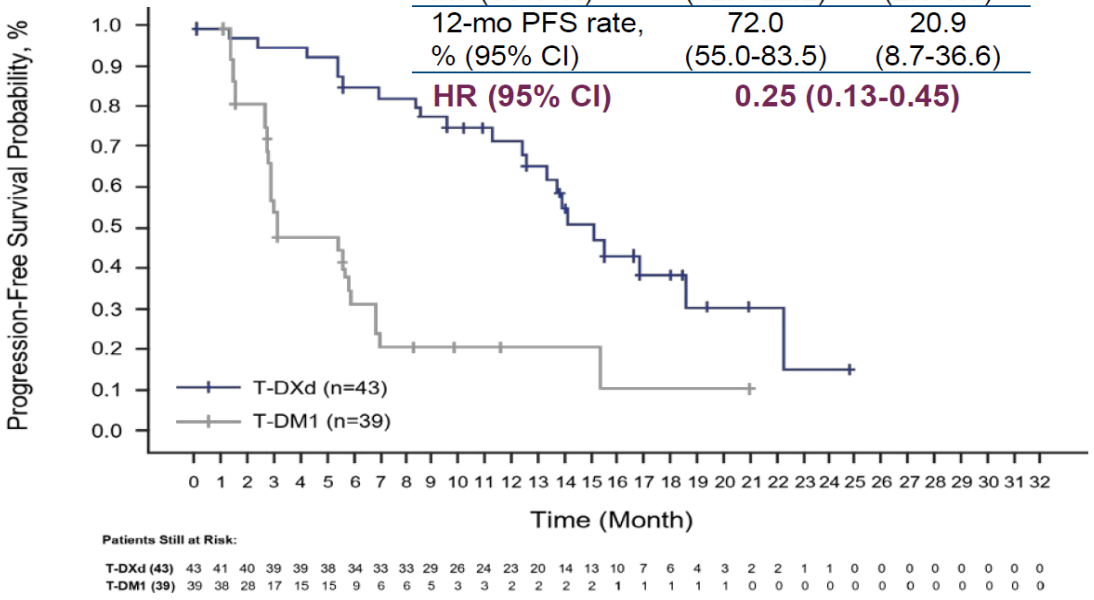
T-Dxd for stable HER2+ BCBM:

sub-analysis of DESTINY-Breast03

Inclusion criteria: <u>stable, treated BM</u>, >2 weeks from RT

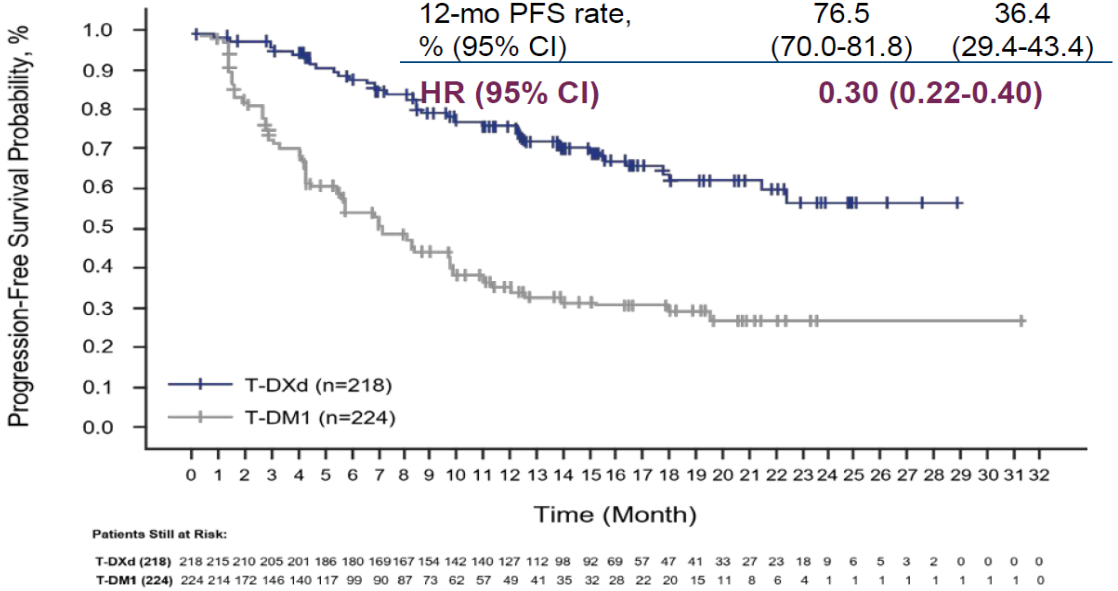
Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	**0.25 (0.13-0.45)**	



No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	**0.30 (0.22-0.40)**	



Intracranial response

	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)

Hurvitz et al., SABCS 2021 GS3-01

T-DXd for active HER2+ BCBM: phase II TUXEDO-1 trial

HER2+ MBC
with newly diagnosed or
progressive brain metastases
N=15

→ Trastuzumab Deruxtecan 5.4mg/kg IV q3wk

Primary endpoint: CNS Response Rate

Bartsch et al, ESMO Breast Cancer 2022

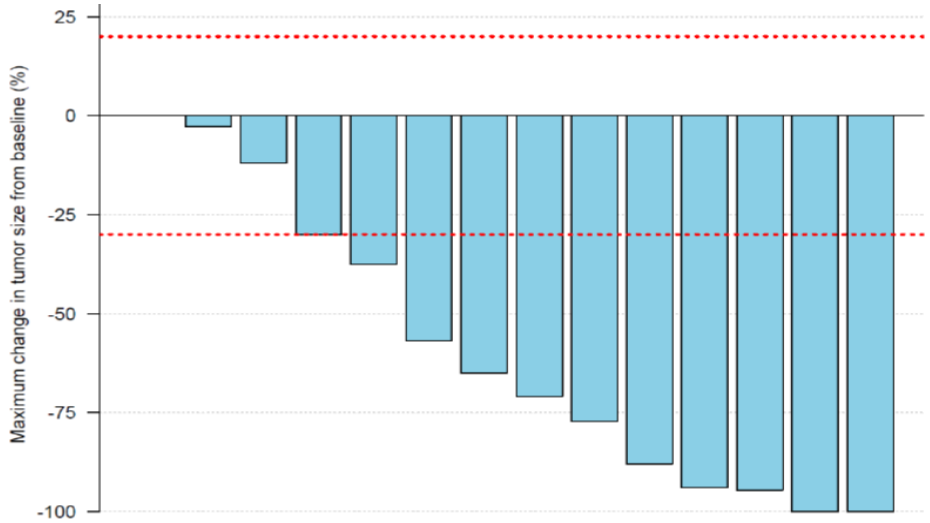
Prior lines of treatment for mBC 2 (1-5); 100% received trast, pert; 60% received T-DM1
Untreated BM 40%, Progressing after local treatment 60%

Objective Response Rate (RANO-BM criteria)

ORR (intention-to-treat population; *n*=15): 73.3% (95% CI 48.1-89.1)

PFS: 14 months (95% CI 11.0-n.r.)

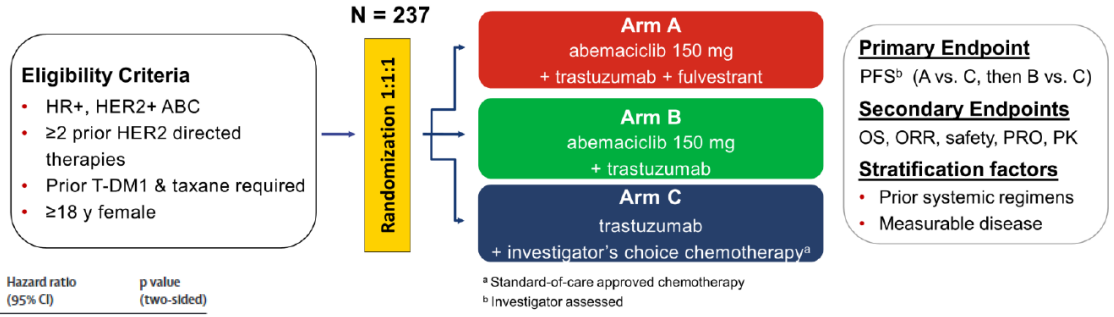
Median follow-up 11 months (range 3 – 17 months)

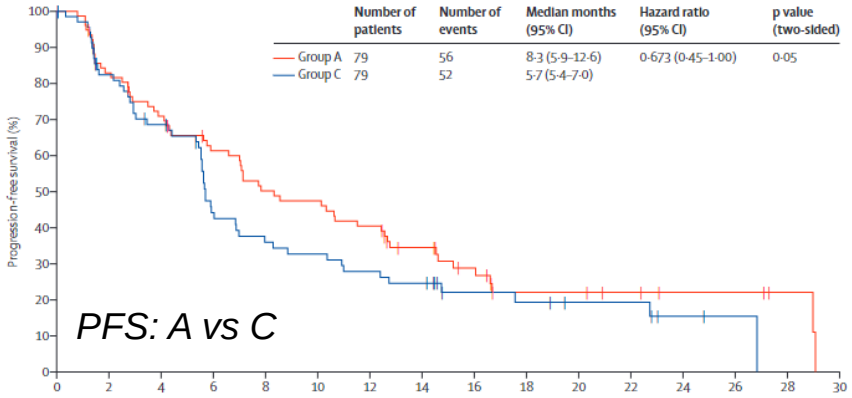


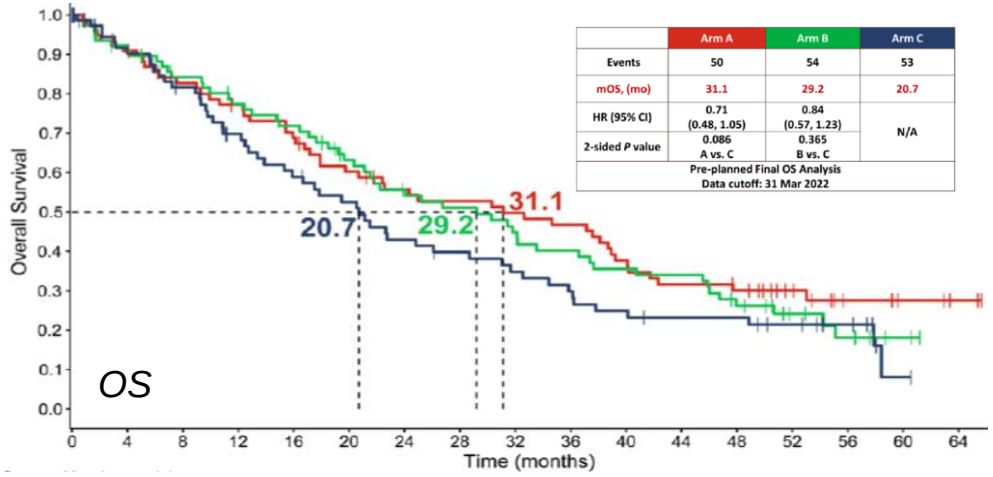
DESTINY BREAST12

Phase IIIb/IV study of **TDXd** in **patients <u>with or without brain metastases</u>** who have **unresectable/advanced or metastatic HER2-positive breast cancer**.

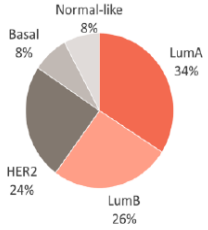
Chemo-free treatment: MonarcHER trial





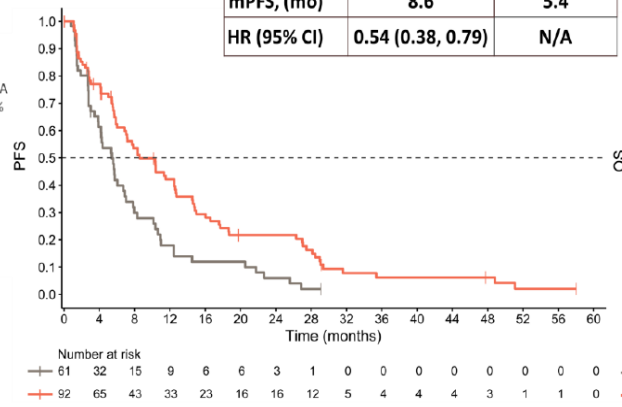


Exploratory RNAseq Analysis – Intrinsic Subtypes



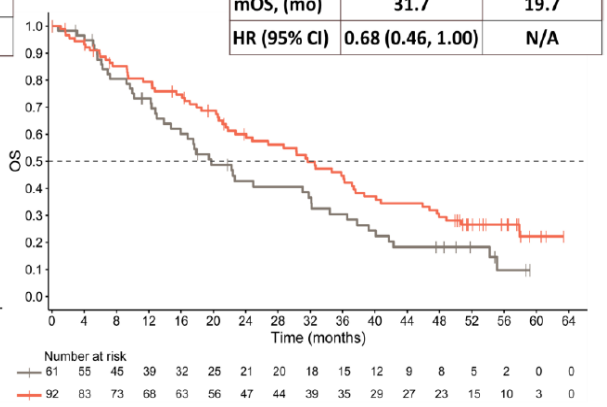
PFS:

	Luminal	Non-luminal
mPFS, (mo)	8.6	5.4
HR (95% CI)	0.54 (0.38, 0.79)	N/A



OS:

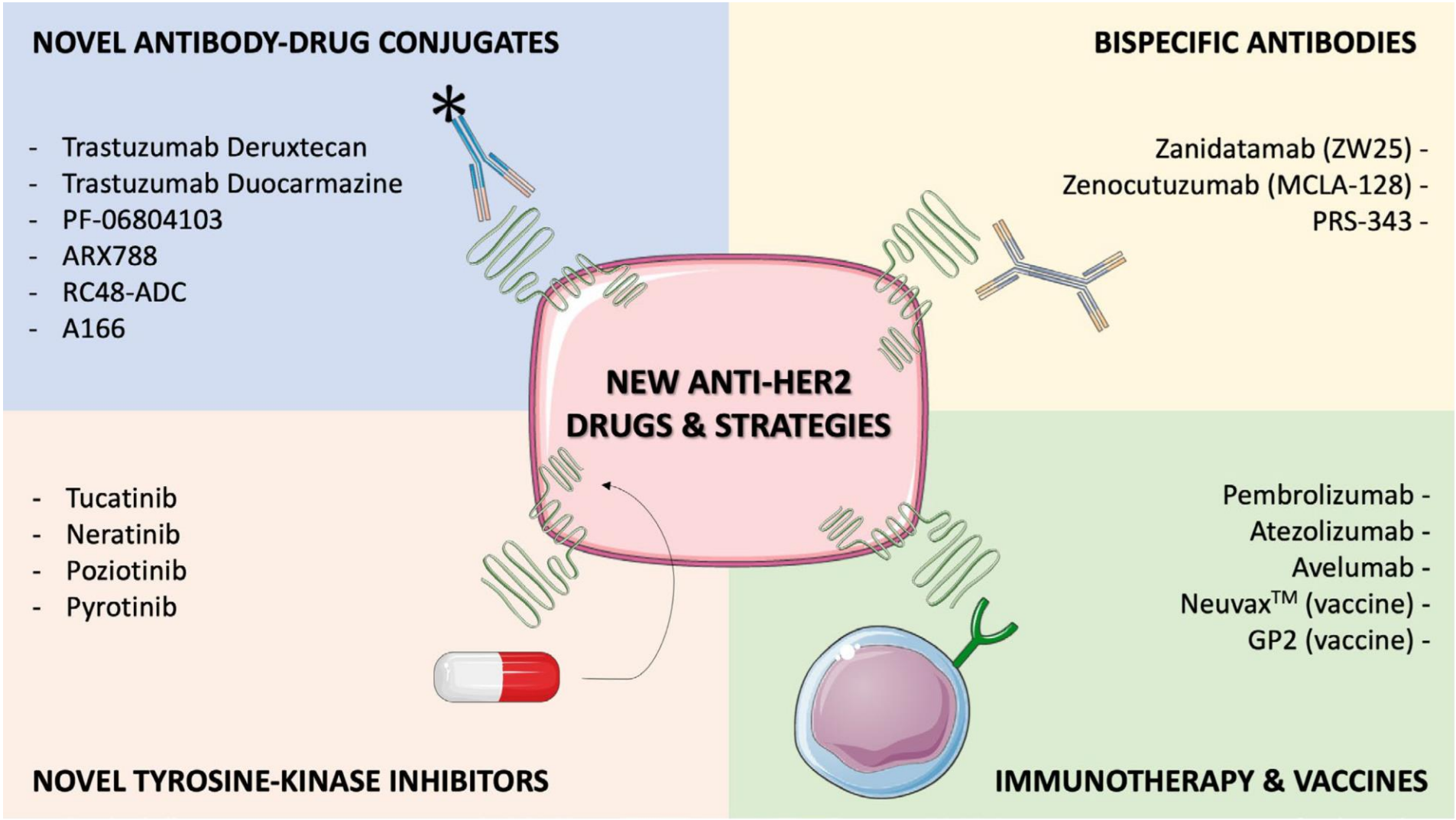
	Luminal	Non-luminal
mOS, (mo)	31.7	19.7
HR (95% CI)	0.68 (0.46, 1.00)	N/A



Luminal subtypes[a] were associated with longer PFS and OS compared to non-luminal.

Tolaney et al, Lancet Oncol 2020; André et al, ESMO 2022

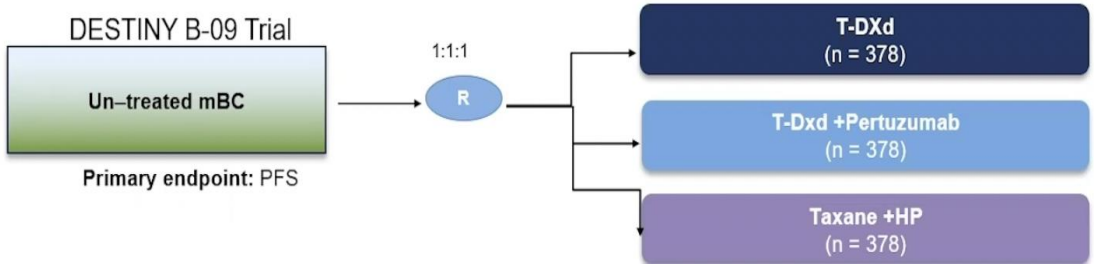
Future perspective in HER2+ MBC



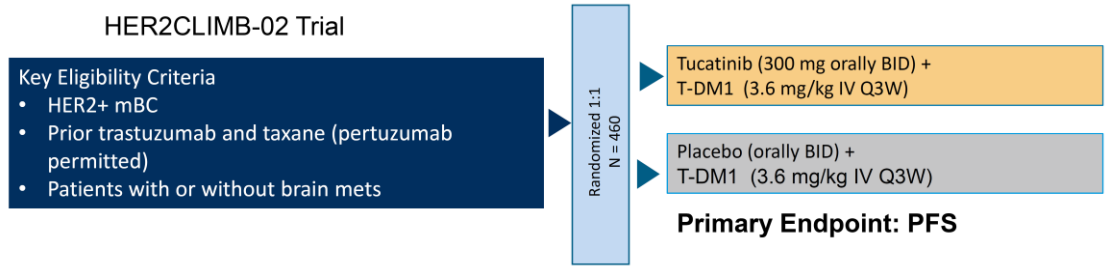
Tarantino P, Morganti S, Curigliano G. *Explor Target Anti-tumor Ther*, 2021; doi:10.37349/etat.2021.00037

Be ready to update our algorithm!

T-Dxd in 1st line

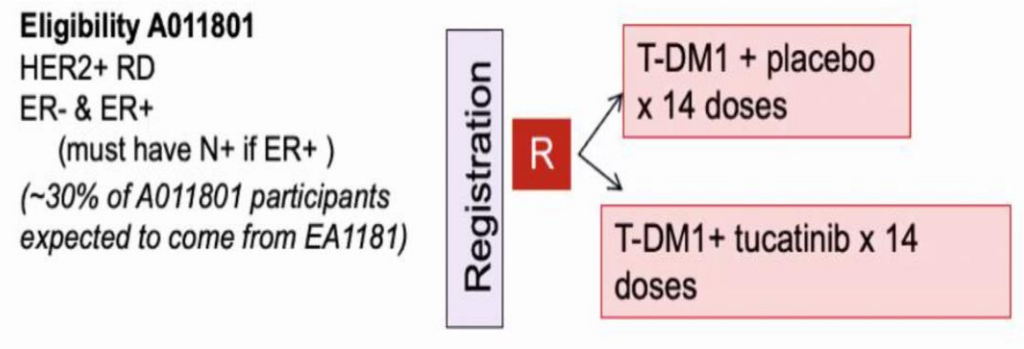


TDM-1 + Tucatinib in early lines

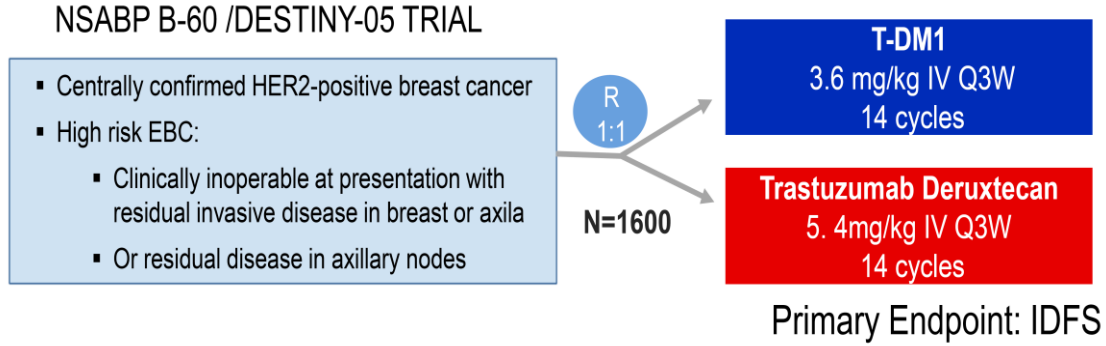


Adjuvant TDM-1 + Tucatinib or T-Dxd in high-risk

COMPASS RESIDUAL DISEASE TRIAL



DESTINY-Breast05



Potential for brain metastases prevention?

DAISY trial: secondary resistance to T-DXD

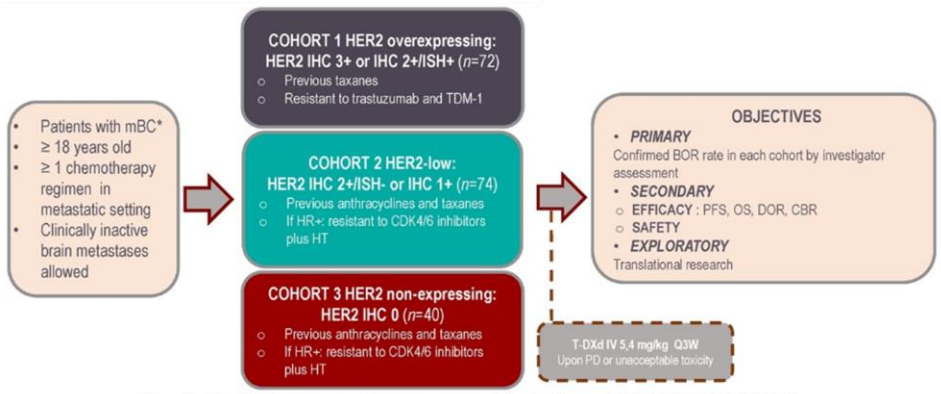
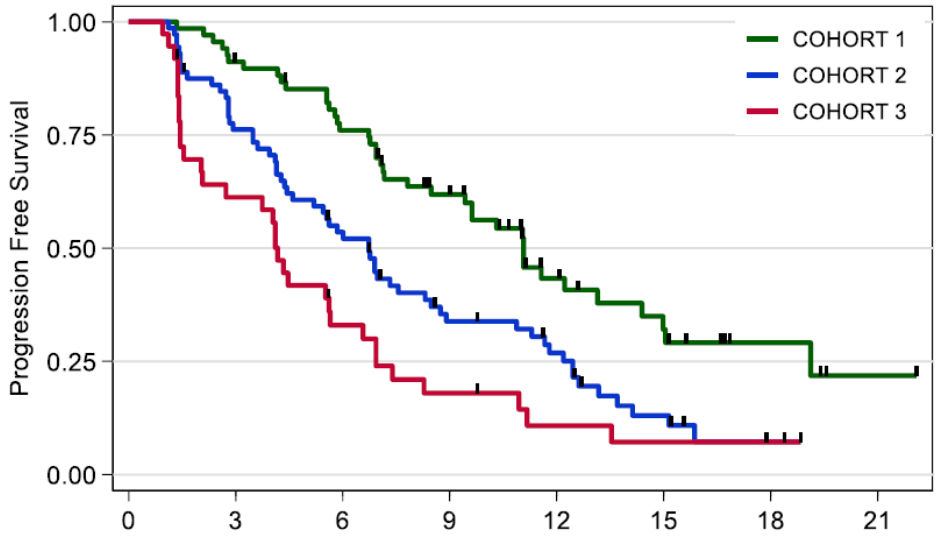
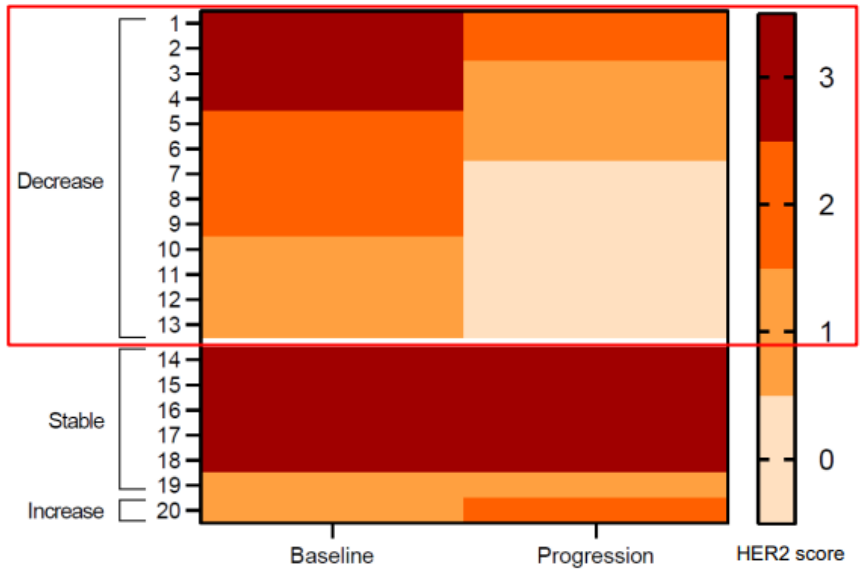


Fig. 1. Study design - multicenter, open-label, phase 2 trial (NCT04132960)



- 25 FFPE samples at baseline and progression: **9** HER2 IHC 3+ or IHC 2+/ISH+; **11** HER2 IHC 2+/ISH- or IHC 1+; **5** IHC 0
- HER2 status by standard IHC



13/20 (65%)
95% CI [40.8-84.6]

13 out of 20 (65%) patients presented a decrease of HER2 expression at progression

5 patients HER2 IHC 0: 4 stable and 1 to IHC

Although HER2 expression is a determinant of T-DXd efficacy, additional mechanisms may also be involved (e.g. SLX4* mutations)

**possibly involved in resistance to the payload (TOP1 inhibition)*

Mosele MF et al., ESMO Breast 2022, Nature Medicine 2023