Deciphering the HER2 Puzzle: Shedding Light on HER2-Positive Breast Cancer and Unraveling Modern Systemic Therapies.

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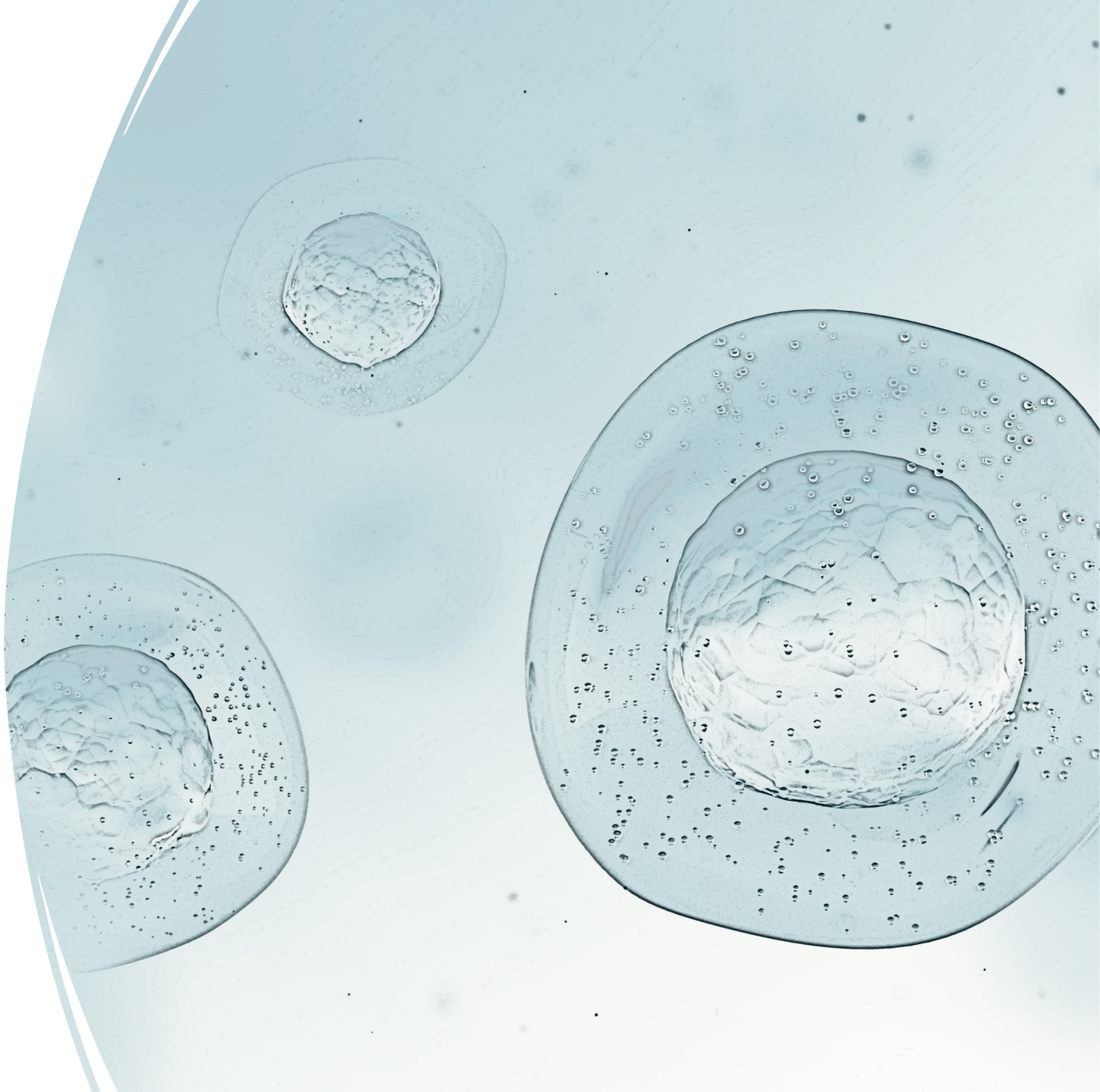
Our Goals for Today

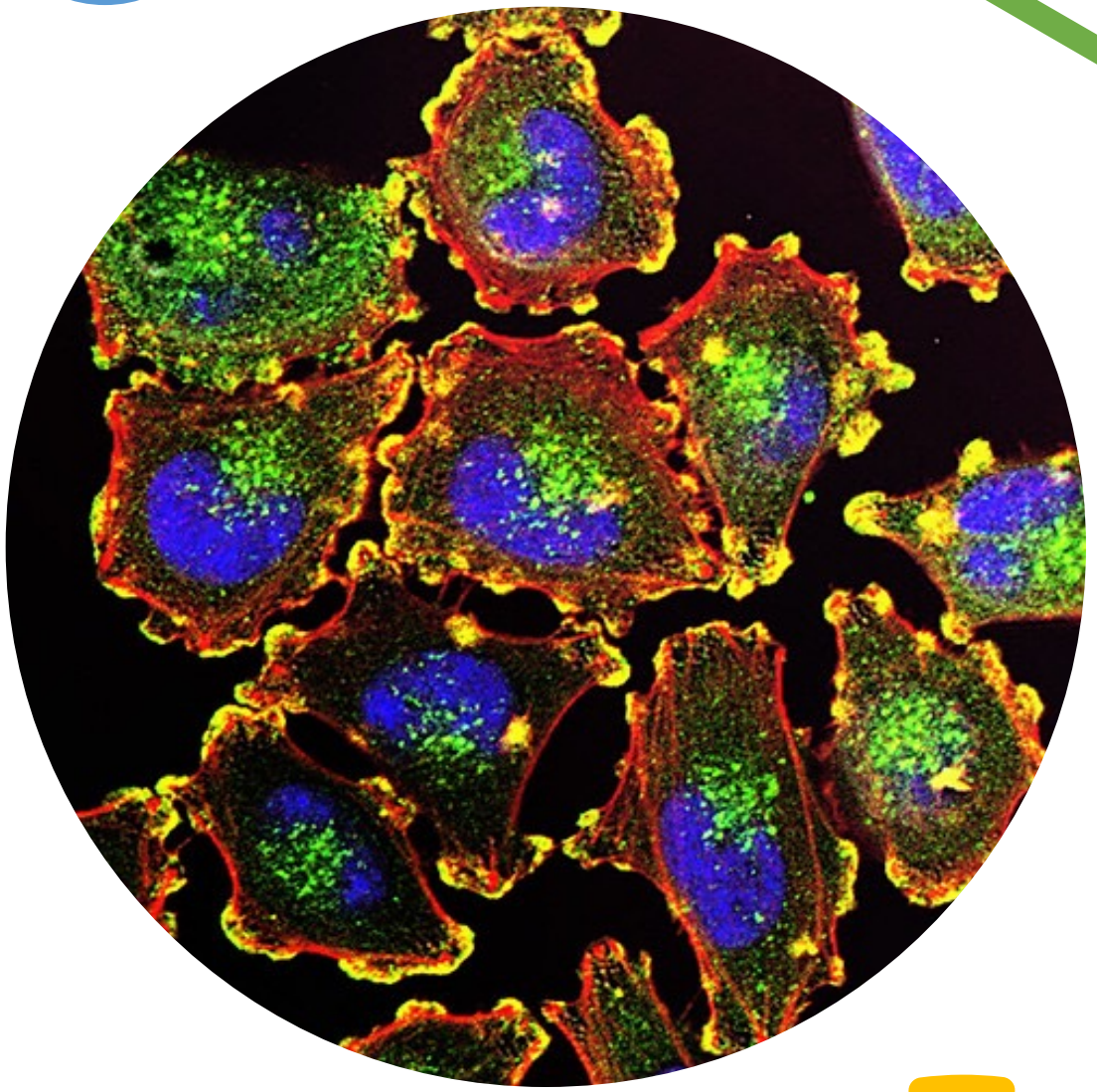
Enhance your knowledge of the current and evolving role of HER2-targeted therapies in HER2-positive breast cancer

Equip all of you with skills to optimally integrate HER2-targeted therapies into individualized treatment plans and help considering sequencing options



Agenda

- Brief history of HER2 & Current Systemic Landscape
- The role of resistance of HER2 therapy & Brain as a Sanctuary Site
- Emerging Therapeutics and diagnostic assays in the HER2 site

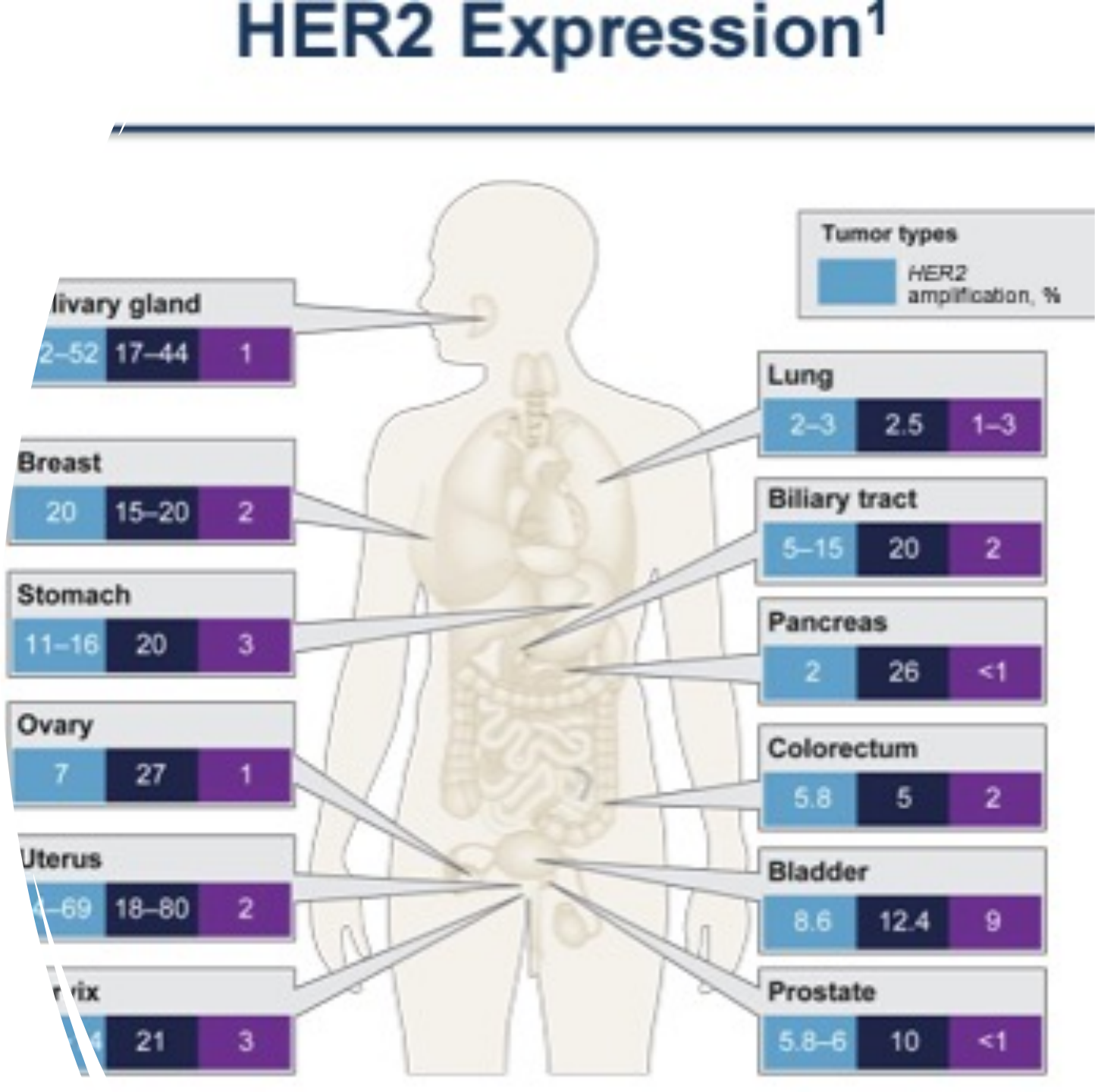


Unlocking the HER2 Code

Illuminating Insights into HER2 positive Breast Cancer and understanding current systemic treatments

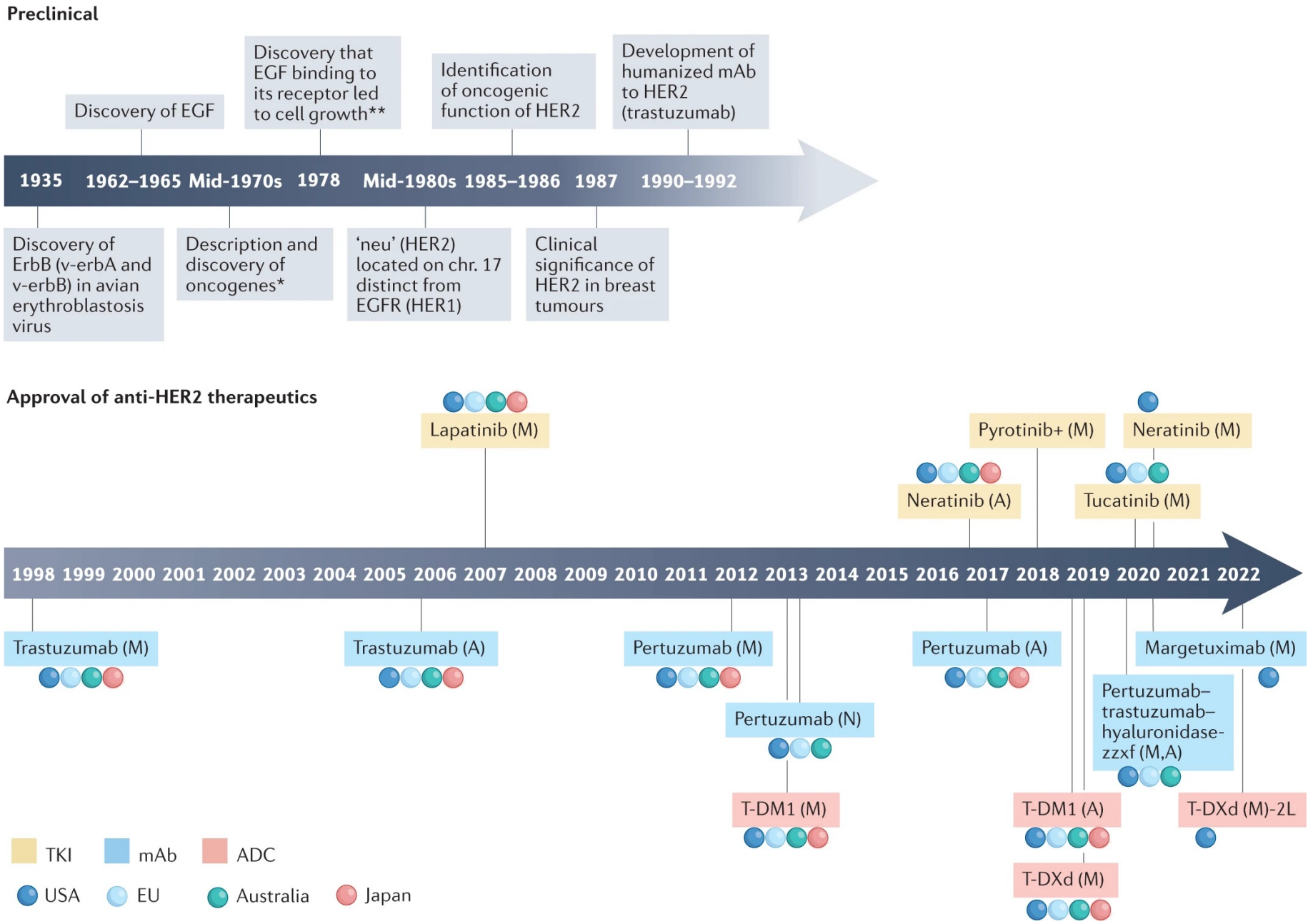
HER2: A excellent oncogenic drug target

- HER2 : control cell growth, proliferation, and survival→ uncontrolled cell division and tumor growth.
- Targeting HER2 can disrupt these signaling pathways, inhibiting tumor progression.
- HER2 : ~15% of all cancers
- HER2 targeted therapies have revolutionized natural history



Advancements in Managing HER2-Positive Breast Cancer: A Growing Arsenal Against a Complex Illness

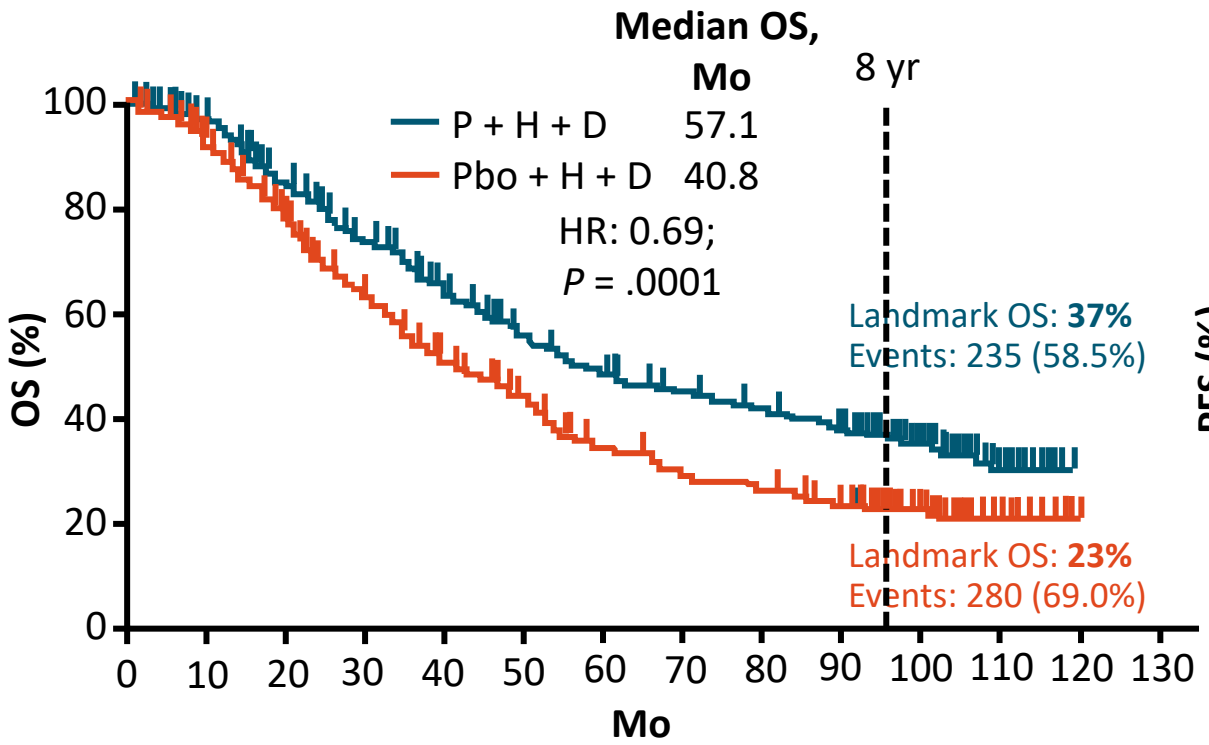
- -HER2 positivity (ASCO–CAP) guidelines, includes tumors that have 3+ positive staining by immunohistochemistry (IHC) in ≥10% of tumour cells, or *HER2* gene amplification detected by fluorescence in situ hybridization (FISH)
- - 'HER2-low' ($HER2^{low}$) : HER2 IHC 1+ by itself or 2+ in the absence of *HER2* gene amplification by ISH (in situ hybridization).



Current Standards of Care in Metastatic Breast Cancer

CLEOPATRA: Survival With Pertuzumab, Trastuzumab, and Docetaxel as 1L Therapy in HER2+ MBC

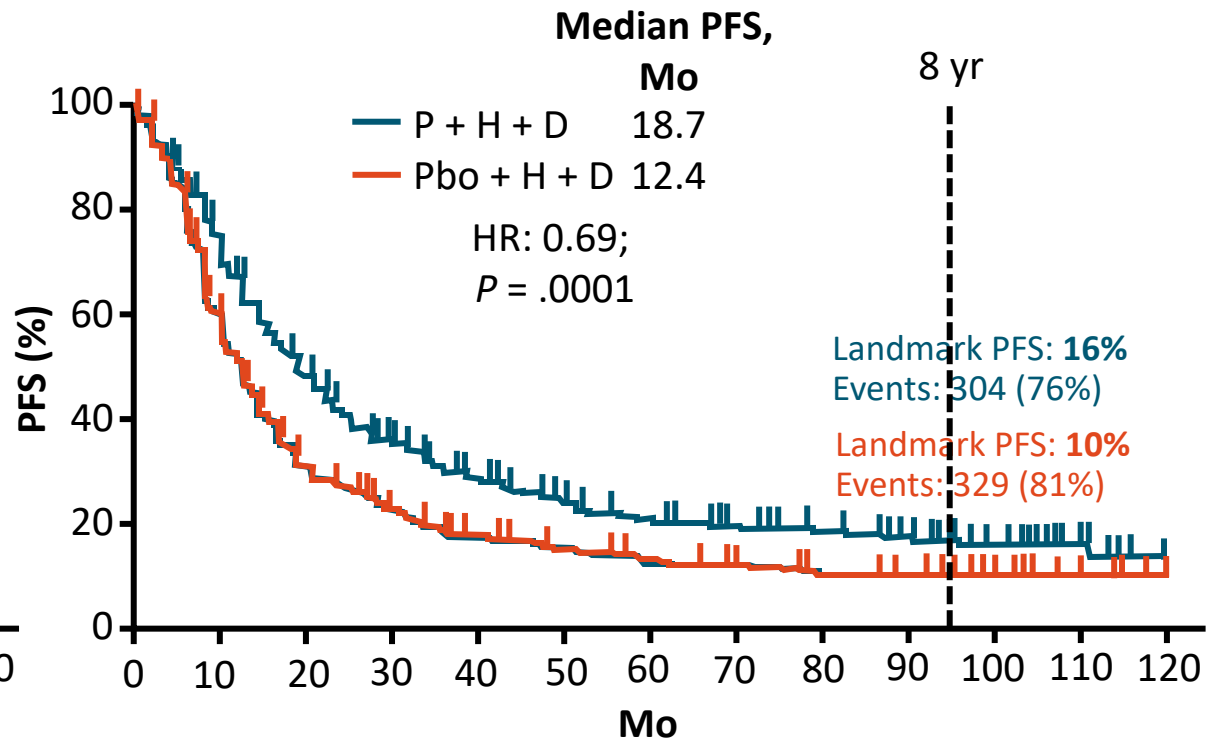
End-of-Study OS in ITT Population*



Patients at Risk, n

P + H + D	402	371	318	269	228	188	165	150	137	120	71	20	0	0
Pbo + H + D	406	350	289	230	181	149	115	96	88	75	44	11	1	0

End-of-Study PFS in ITT Population*

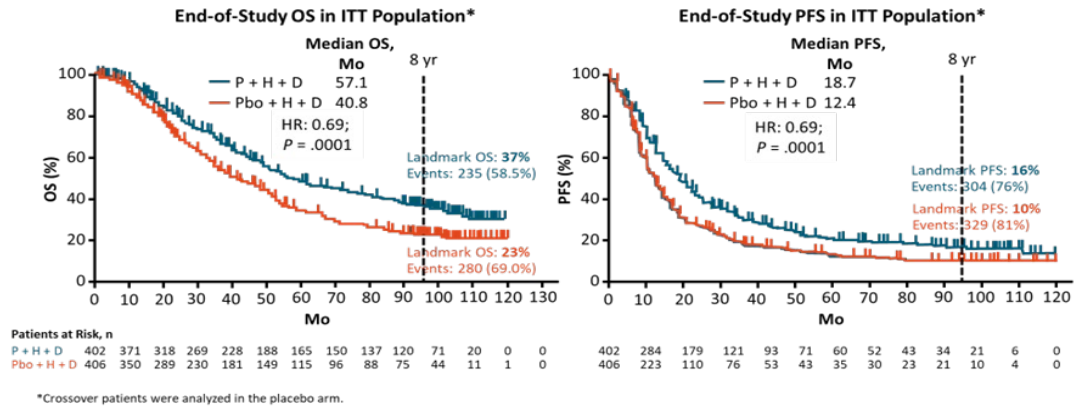


402	284	179	121	93	71	60	52	43	34	21	6	0
406	223	110	76	53	43	35	30	23	21	10	4	0

*Crossover patients were analyzed in the placebo arm.

Swain. Lancet Oncol. 2020;21:519.

CLEOPATRA: Survival With Pertuzumab, Trastuzumab, and Docetaxel as 1L Therapy in HER2+ MBC



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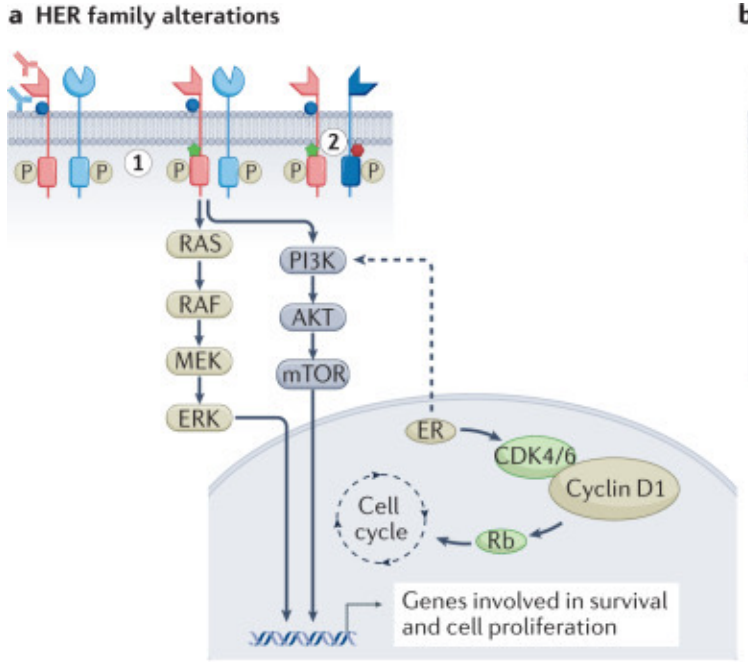
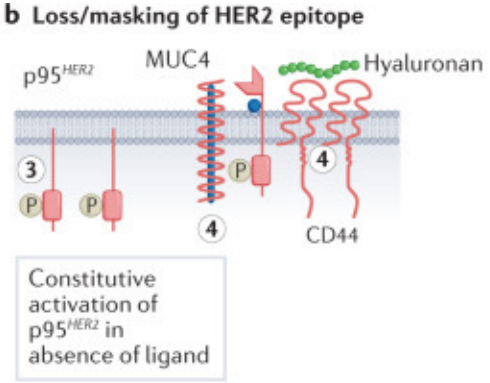
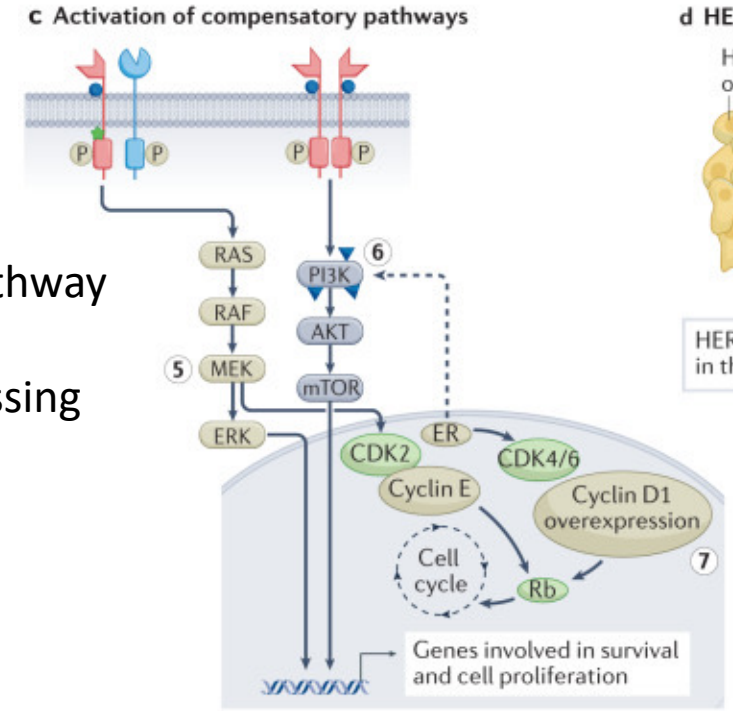
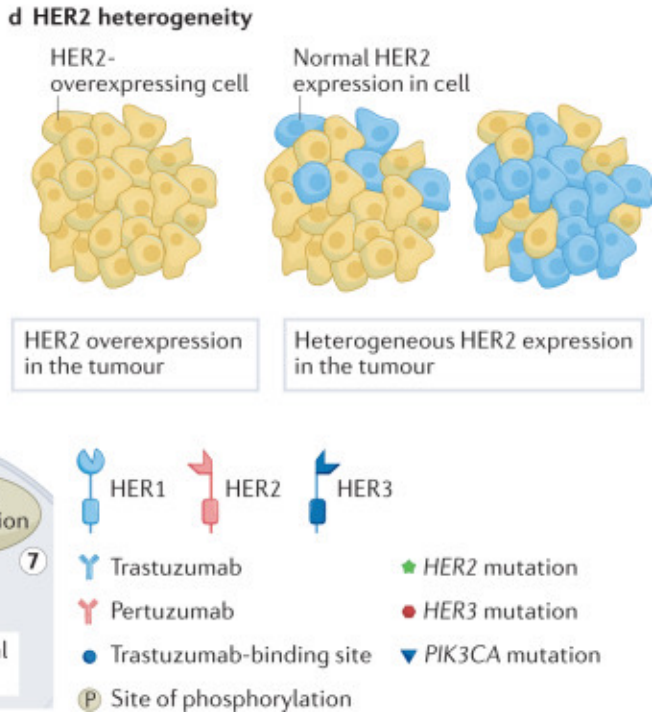




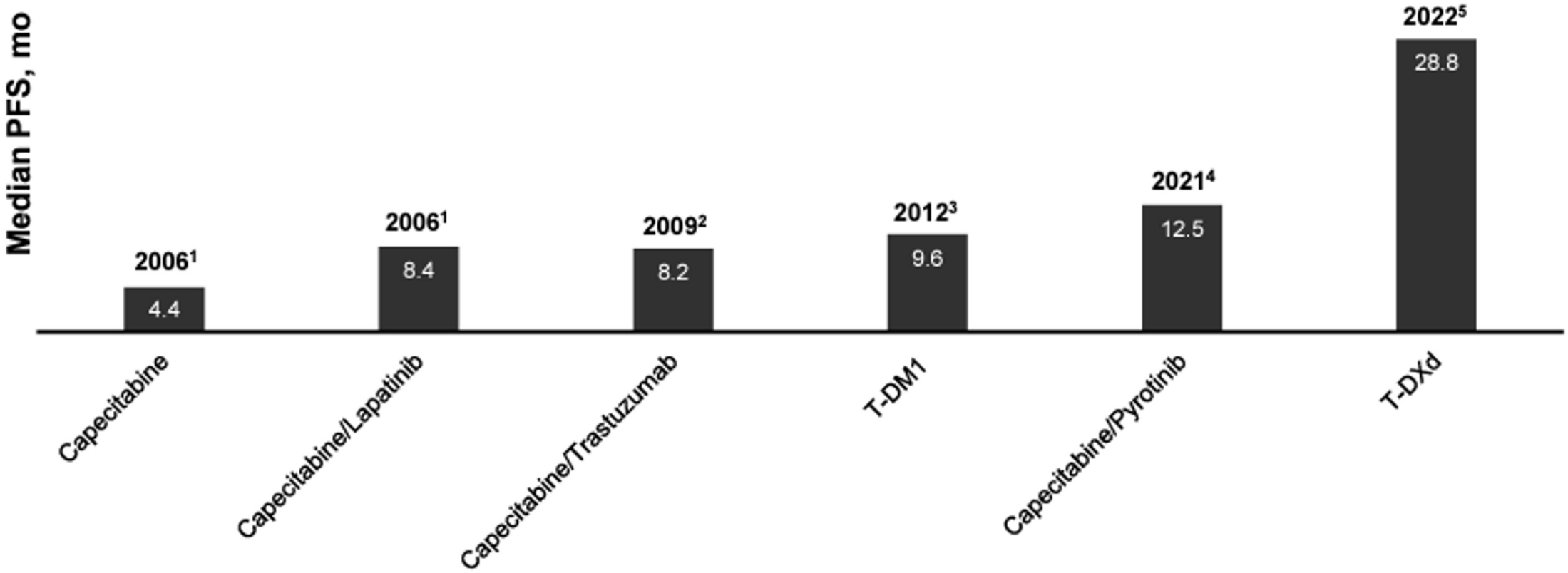
So why are we not seeing more durable responses long term with taxane + trastuzumab and pertuzumab?

- Mutations in *HER2* → P13K– AKT and RAS–MAPK pathway activation.
- Loss of HER2 extracellular domain in cells overexpressing p95*HER2* receptor.
- Loss of HER2 epitope
- HER family alterations





How do we improve the next generation of TKI's to help us get durable responses?

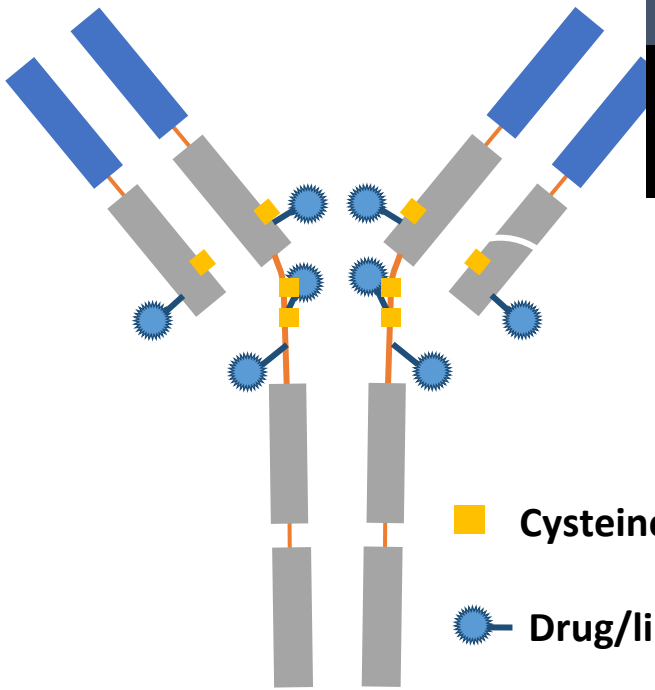


Characteristic Differences Between T-DXd and T-DM1

ADC Attribute	T-DXd[1-4*]	T-DM1[3-6]
Payload mechanism of action	Topoisomerase I inhibitor	Anti-microtubule
Drug-to-antibody ratio	~8:1	~3.5:1
With tumor-selective cleavable linker	Yes	No
With evidence of bystander antitumor effect	Yes	No

*Clinical relevance of these features is under investigation.

T-DXd



Cys

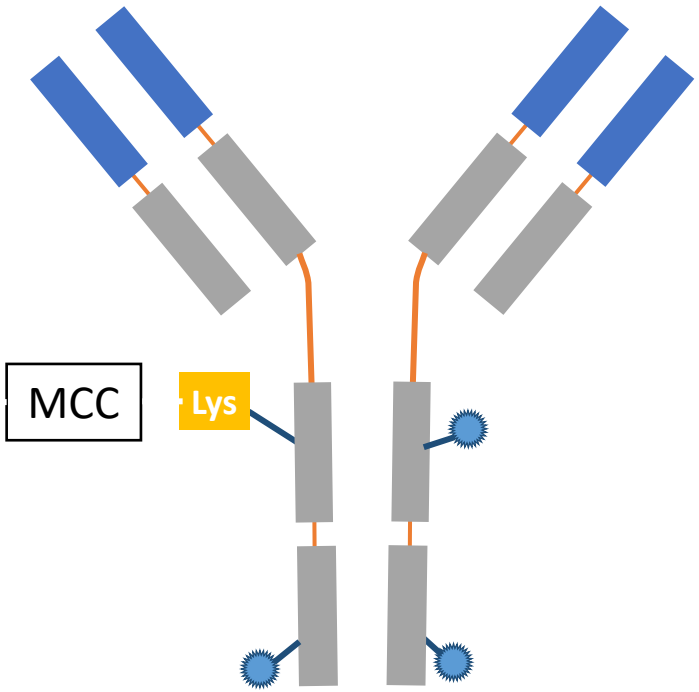
Deruxtecan

DXd

Cysteine residue

Drug/linker

T-DM1



DM1

MCC

Lys

Both are HER2-targeting ADCs with a similar monoclonal antibody backbone

1. Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. 2. Ogitani. Clin Cancer Res. 2016;22:5097. 3. Trail. Pharmacol Ther. 2018;181:126.
4. Ogitani. Cancer Sci. 2016;107:1039. 5. LoRusso. Clin Cancer Res. 2011;17:6437. 6. Barok. Breast Cancer Res. 2014;16:209.

DESTINY-Breast03: T-DXd vs T-DM1 in Previously Treated HER2+ MBC

- Randomized, multicenter, open-label phase III study (data cutoff: July 25, 2022)

Stratified by HR status, prior treatment with pertuzumab, history of visceral disease

Patients with unresectable or metastatic HER2+ breast cancer; previous trastuzumab + taxane tx in metastatic setting or (neo)adjuvant with recurrence ≤6 mo of tx; ECOG PS 0/1
(N = 524)

Trastuzumab Deruxtecan
5.4 mg/kg IV Q3W
(n = 261)

Trastuzumab Emtansine
3.6 mg/kg IV Q3W
(n = 263)

Median Follow-up

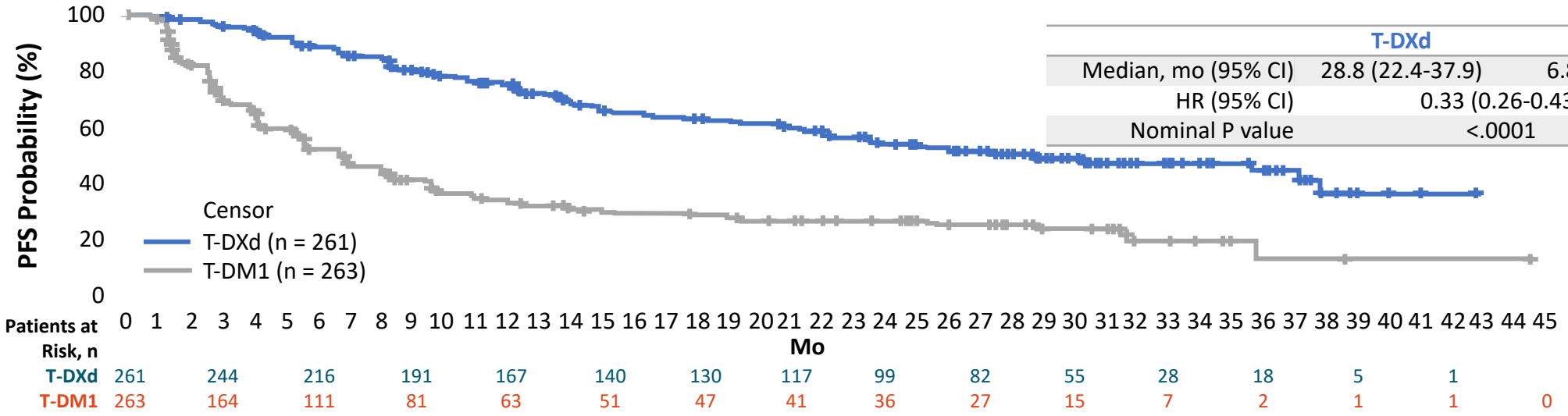
T-DXd: 28.4 mo

T-DM1: 26.5 mo

- **Primary endpoint:** PFS by BICR
- **Key secondary endpoint:** OS
- **Other secondary endpoints**: ORR (BICR and investigator), DoR (BICR), safety

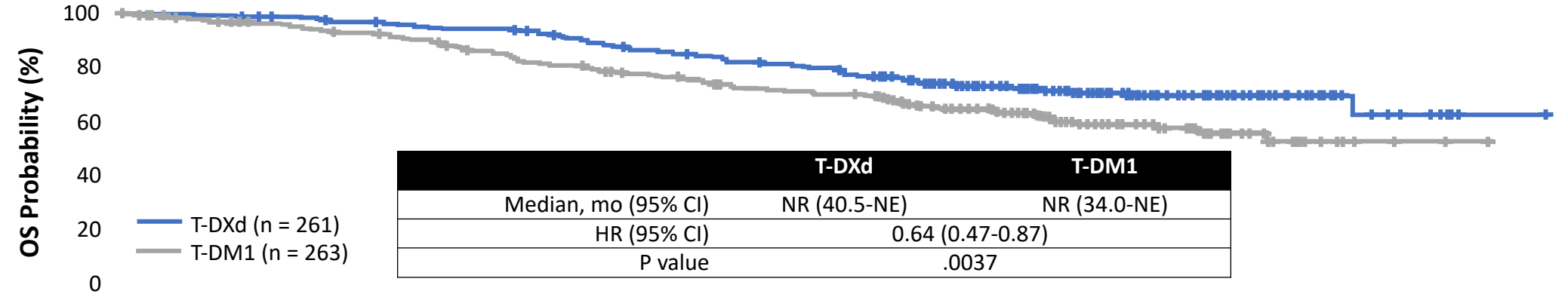
Hurvitz Lancet. 2023;401:105. Hurvitz. SABCS 2022. Abstr GS2-02.

DESTINY-Breast03: Updated PFS and OS



	T-DXd	T-DM1
Median, mo (95% CI)	28.8 (22.4-37.9)	6.8 (5.6-8.2)
HR (95% CI)	0.33 (0.26-0.43)	
Nominal P value	<.0001	

Patients at Risk, n																
T-DXd	261	244	216	191	167	140	130	117	99	82	55	28	18	5	1	
T-DM1	263	164	111	81	63	51	47	41	36	27	15	7	2	1	1	0



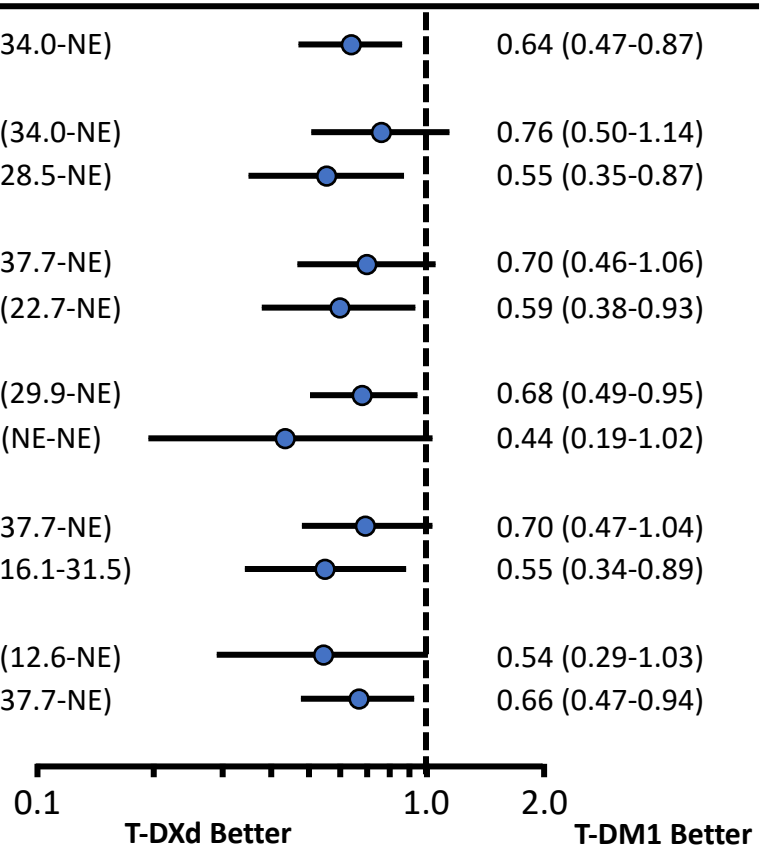
	T-DXd	T-DM1
Median, mo (95% CI)	NR (40.5-NE)	NR (34.0-NE)
HR (95% CI)	0.64 (0.47-0.87)	
P value	.0037	

Patients at Risk, n																	
T-DXd	261	255	249	241	236	224	211	200	187	156	109	64	38	18	7	1	0
T-DM1	263	248	237	227	211	197	183	169	164	129	90	45	27	8	3	1	

Hurvitz Lancet. 2023;401:105. Hurvitz. SABCS 2022. Abstr GS2-02.

DESTINY-Breast03: Updated OS by Subgroup

	Events, n/N		Median OS, Mo (95% CI)		HR for Death (95% CI)
	Trastuzumab Deruxtecan	Trastuzumab Emtansine	Trastuzumab Deruxtecan	Trastuzumab Emtansine	
All patients	72/261	97/263	NR (40.5-NE)	NR (34.0-NE)	0.64 (0.47-0.87)
Hormone receptor status					
Positive	42/133	51/139	NR (40.5-NE)	37.7 (34.0-NE)	0.76 (0.50-1.14)
Negative	30/126	45/122	NR (NE-NE)	NR (28.5-NE)	0.55 (0.35-0.87)
Previous pertuzumab					
Yes	41/162	50/158	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.46-1.06)
No	31/99	47/105	NR (NE-NE)	31.5 (22.7-NE)	0.59 (0.38-0.93)
Baseline visceral disease					
Yes	64/195	80/189	NR (40.5-NE)	35.4 (29.9-NE)	0.68 (0.49-0.95)
No	8/66	17/74	NR (NE-NE)	NR (NE-NE)	0.44 (0.19-1.02)
Previous lines of systemic therapy*					
<3	44/188	57/191	NR (40.5-NE)	NR (37.7-NE)	0.70 (0.47-1.04)
≥3	28/73	40/72	NR (27.4-NE)	22.8 (16.1-31.5)	0.55 (0.34-0.89)
Baseline brain metastases					
Yes	17/43	22/39	NR (23.8-NE)	25.1 (12.6-NE)	0.54 (0.29-1.03)
No	55/218	75/244	NR (40.5-NE)	NR (37.7-NE)	0.66 (0.47-0.94)



*Not including hormone therapy.

Hurvitz Lancet. 2023;401:105.

DESTINY-Breast03: Updated Overall Safety

Safety Outcome	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE, n(%)	252 (98.1)	228 (87.4)
▪ Grade ≥3	121 (47.1)	110 (42.1)
▪ Serious	33 (12.8)	20 (7.7)
Drug-related TEAE associated with the following, n (%)		
▪ Discontinuation	51 (19.8)	17 (6.5)
▪ Dose reduction	65 (25.3)	38 (14.6)
▪ Drug interruption	108 (42.0)	45 (17.2)
▪ Outcome of death	0 (0)	0 (0)
Median treatment duration, mo (range)	18.2 (0.7-44.0)	6.9 (0.7-39.3)

AE of Special Interest, n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Drug-related ILD/pneumonitis	39 (15.2)	8 (3.1)
▪ Grade 1	11 (4.3)	4 (1.5)
▪ Grade 2	26 (10.1)	3 (1.1)
▪ Grade 3	2 (0.8)	1 (0.4)
▪ Grade 4	0	0
▪ Grade 5	0	0

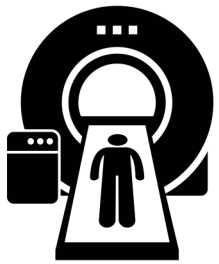
- With longer treatment exposure, rates of ILD/pneumonitis increased from 10.5% at interim analysis to 15.2%
  - 4 additional grade 1 events
  - 8 additional grade 2 events
- Overall incidence of grade 3 events (0.8%) unchanged from interim analysis
- Rates of drug-related grade ≥3 TEAEs were similar between arms
- Most common drug-related TEAEs associated with treatment discontinuation:
  - T-DXd: pneumonitis (5.8%), ILD (5.1%), pneumonia (1.9%)
  - T-DM1: decreased platelet count (1.5%), pneumonitis (1.1%), thrombocytopenia (1.1%)

Hurvitz. SABCS 2022. Abstr GS2-02. Cortes. NEJM. 2022;386:1143

Management of ILD Associated With T-DXd: "Five S Rules"

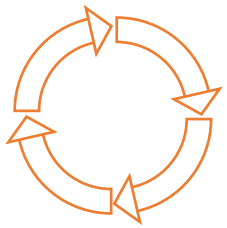
Screen

- Careful selection of patient needed → T-DXd initiation to optimize monitoring based on the BL risk
- Continue screening during therapy + regular clinical evaluations to exclude symptoms and signs of ILD



Scan

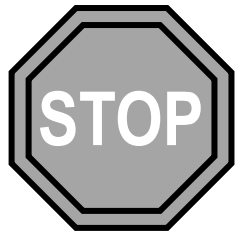
- Radiologic scans are the fundamental diagnostic tools for ILD; preference is for high-resolution chest CT scans
- At baseline, a scan is recommended + regular repeat scans every 6-12 wk



Synergy

ILD risk minimization requires team efforts, including patient education and education of healthcare team

Multidisciplinary management is warranted once ILD is suspected



Suspend Treatment

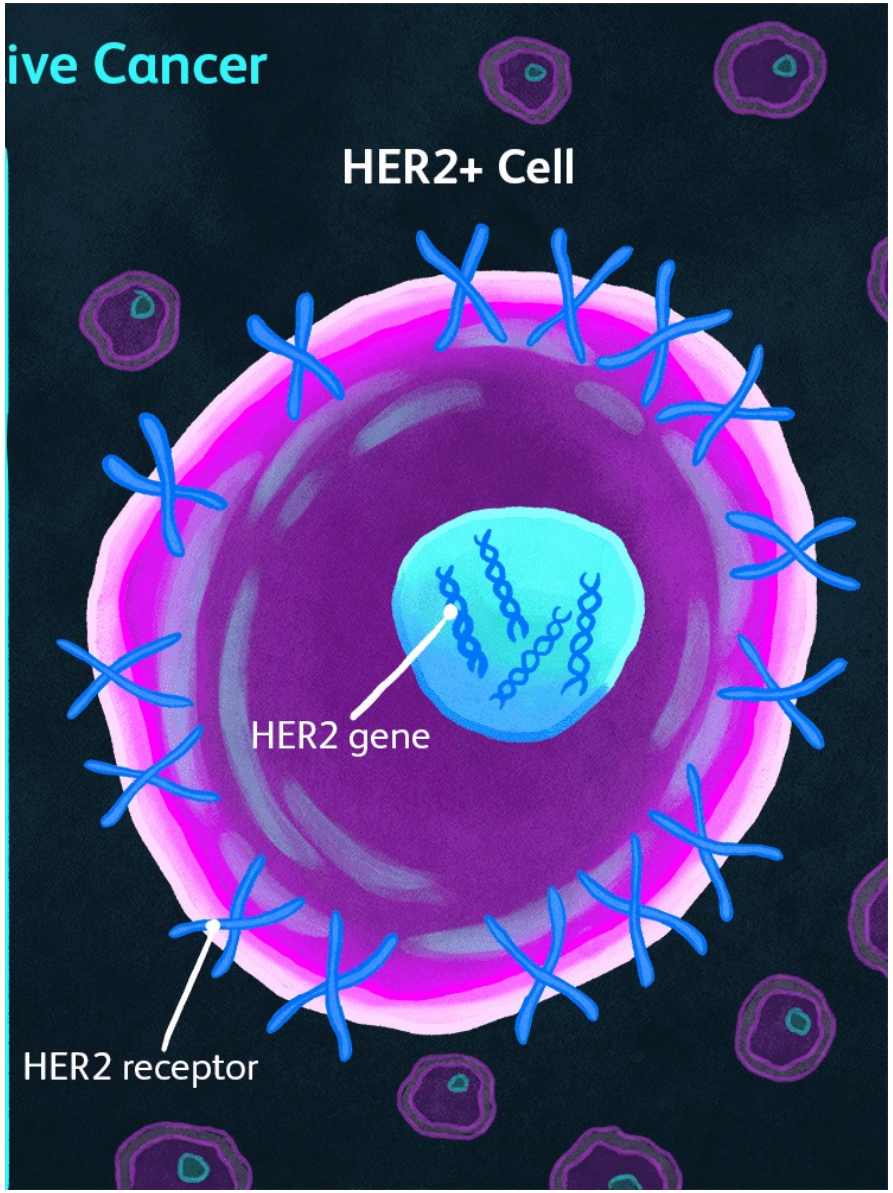
- Once ILD is suspected, T-DXd should always be interrupted
- T-DXd should only be restarted in the case of asymptomatic ILD that fully resolves

Steroids

- Mainstay for the treatment of T-DXd–associated ILD is the administration of corticosteroids
- Corticosteroid dose should be adapted according to the toxicity grade

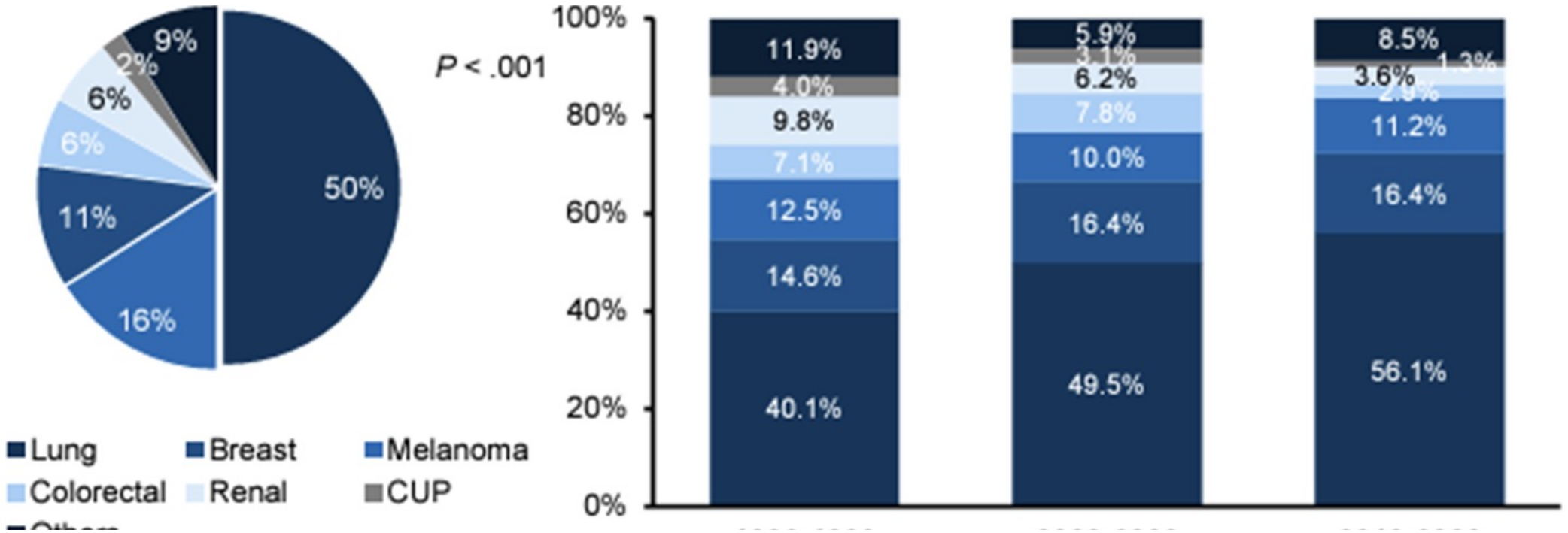
Adapted from Tarantino. JCO Oncol Pract. 2023;19:526.

Brain Metastases in HER2 positive Breast Cancer



Brain Mets and Resistance

- Breast cancer is one of the most common causes of BM and LMC
- The incidence in HER2-positive tumors is 20%-30% and is associated with better prognosis than in other subtypes of breast cancer
- There are different options to treat BM depending on several factors



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Multidisciplinary Tumor Board

In Favor of Local Strategies

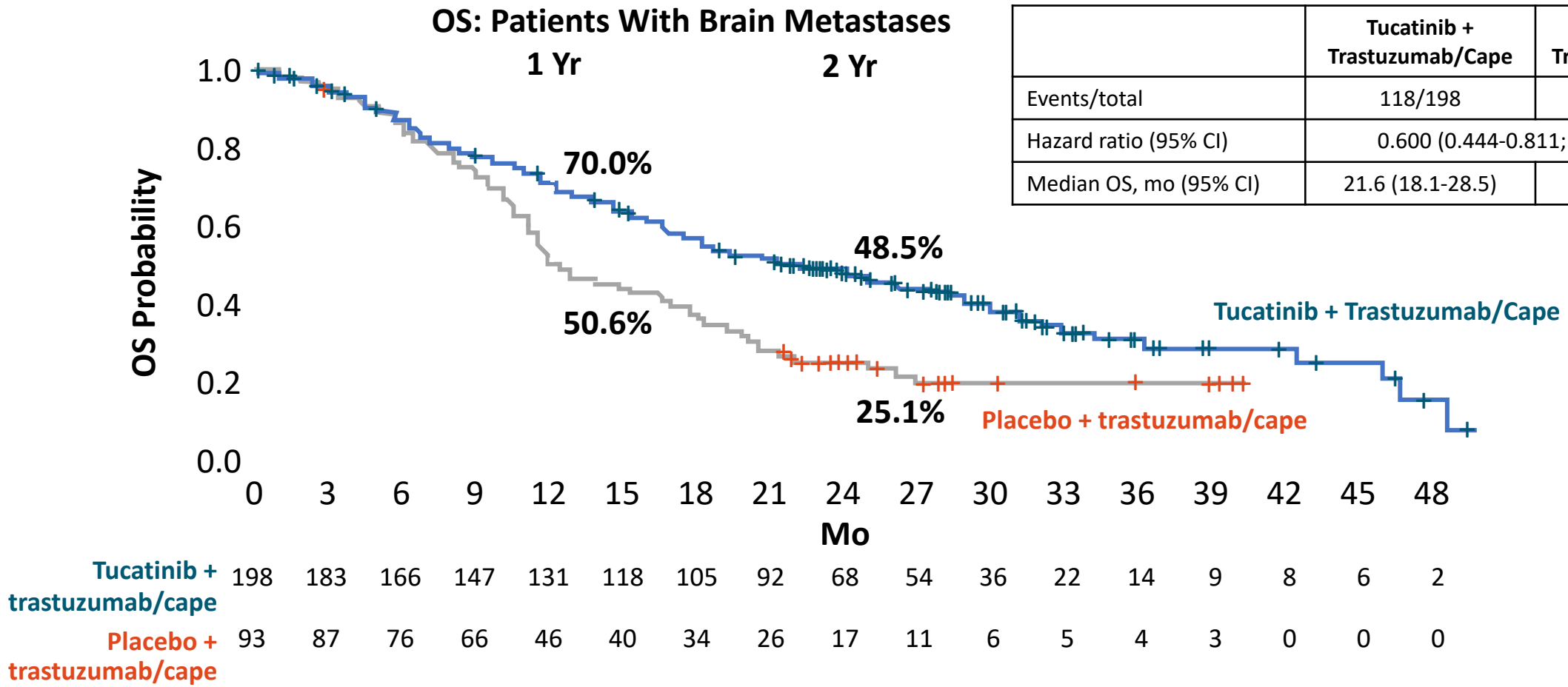
- Neurological symptoms
- <10 lesions (maybe radiation oncologists will say more!) → SRS or surgery
- Big lesions
- "Bad" localization (cerebellar lesions)
- Important edema
- Need for tissue

Medical oncologists
Radiation oncologists
Neurosurgeons
Neuroradiologists
Pathologists

In Favor of Systemic Therapies

- HER2+ subtype
- Asymptomatic disease
- Good drugs (with evidence of CNS activity) available
- Previous radiation

HER2CLIMB: OS in All Patients With Brain Metastases



	Tucatinib + Trastuzumab/Cape	Placebo + Trastuzumab/Cape
Events/total	118/198	71/93
Hazard ratio (95% CI)	0.600 (0.444-0.811; P = .00078)	
Median OS, mo (95% CI)	21.6 (18.1-28.5)	12.5 (11.2-16.9)

Improved OS benefit with longer follow-up: previous analysis OS 18.1 mo vs 12.0 mo

Lin. SABCS 2021. Abstr PD4.04. Lin. JAMA Oncol. 2022;[Epub].

HER2CLIMB: Intracranial Overall Response and Duration of Response in Patients With Active Brain Metastases

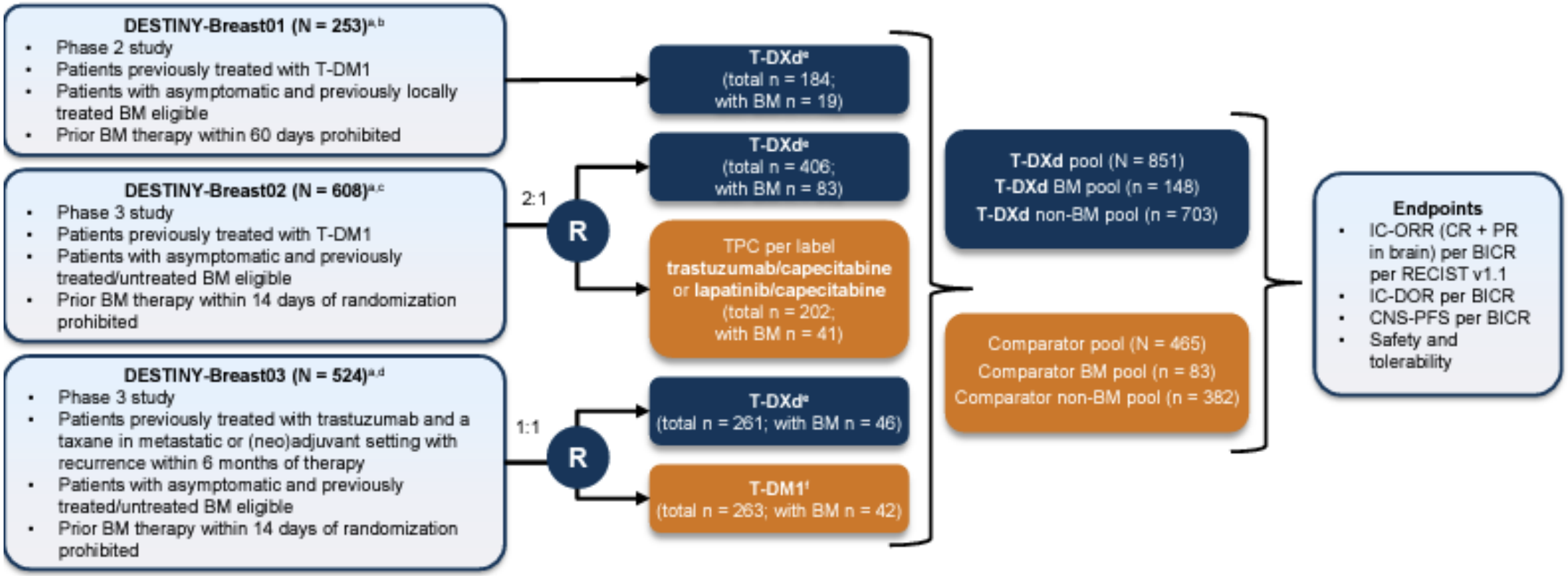
	Tucatinib + Trastuzumab/Cape (n = 55)	Placebo + Trastuzumab/Cape (n = 20)
Patients with CR or PR, n	26	4
Confirmed ORR-IC, % (95% CI)	47.3 (33.7-61.2)	20.0 (5.7-43.7)
DoR-IC mo, (95% CI)*	8.6 (5.5-10.3)	3.0 (3.0-10.3)

Patients had active brain mets and measurable IC lesions at baseline

*Calculated using Collet and colleagues 1994 complementary log-log transformation method.

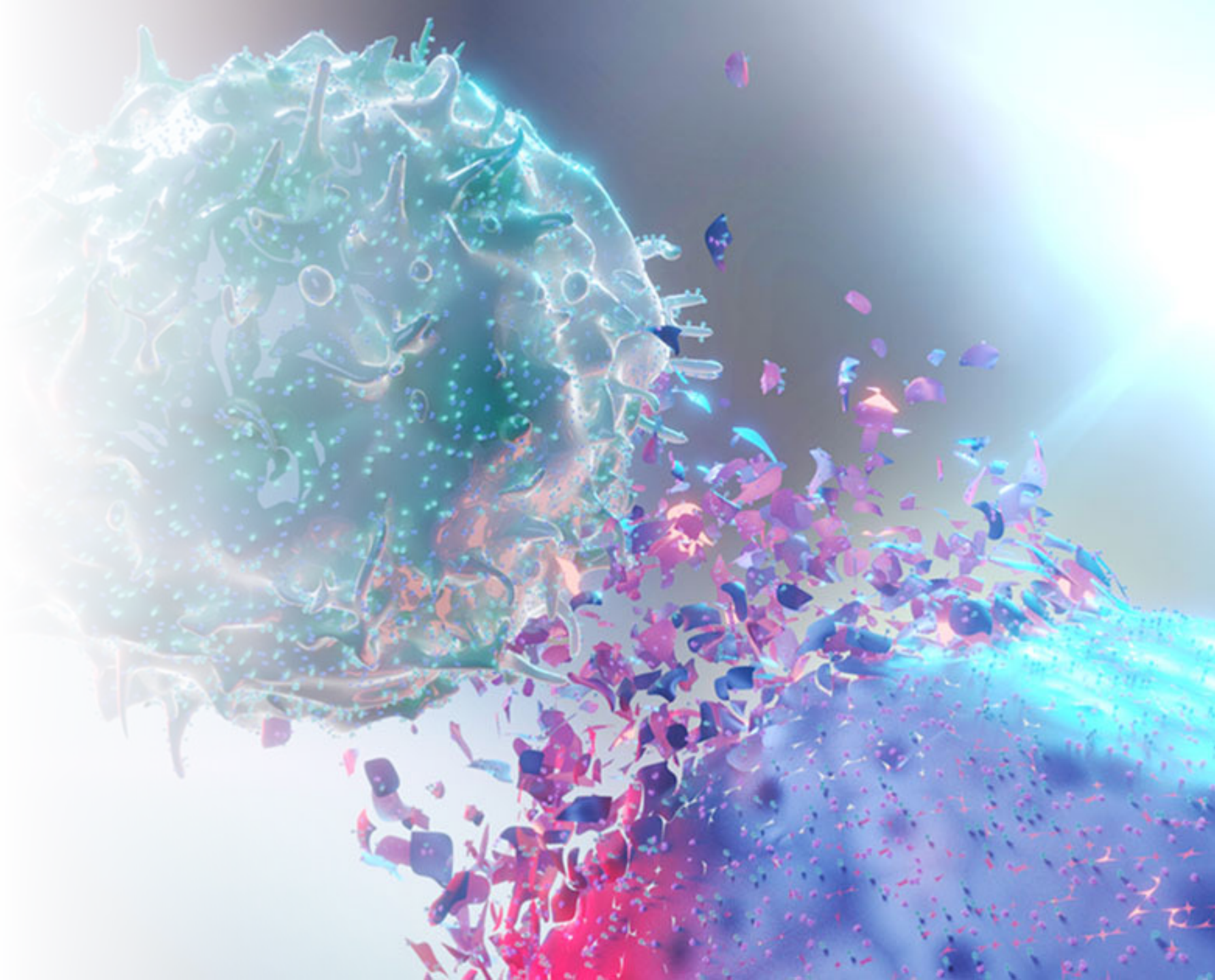
Lin. SABCS 2021. Abstr PD4.04. Lin. JAMA Oncol. 2022;[Epub].

Pooled Analysis of T-DXd in HER2+ MBC With Brain Metastases From DESTINY-Breast01, 02, and 03[1]



The BM and non-BM pools were determined by BICR at baseline among all patients based on mandatory brain CT/MRI screening

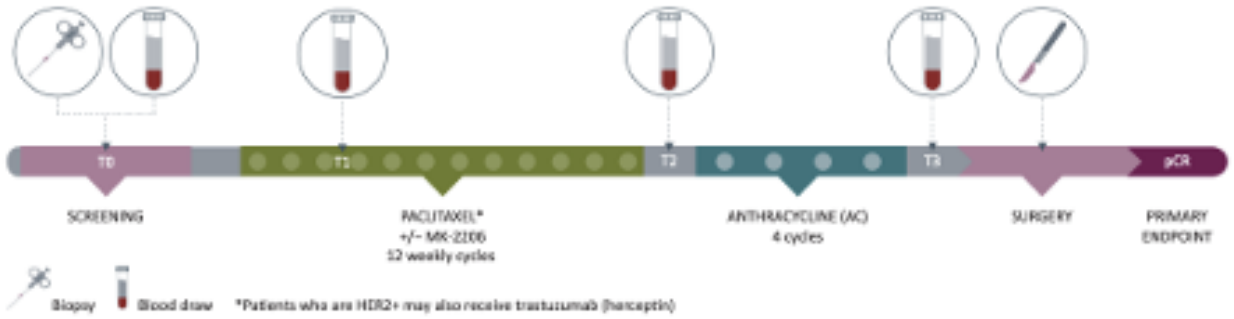
Emerging New Concepts

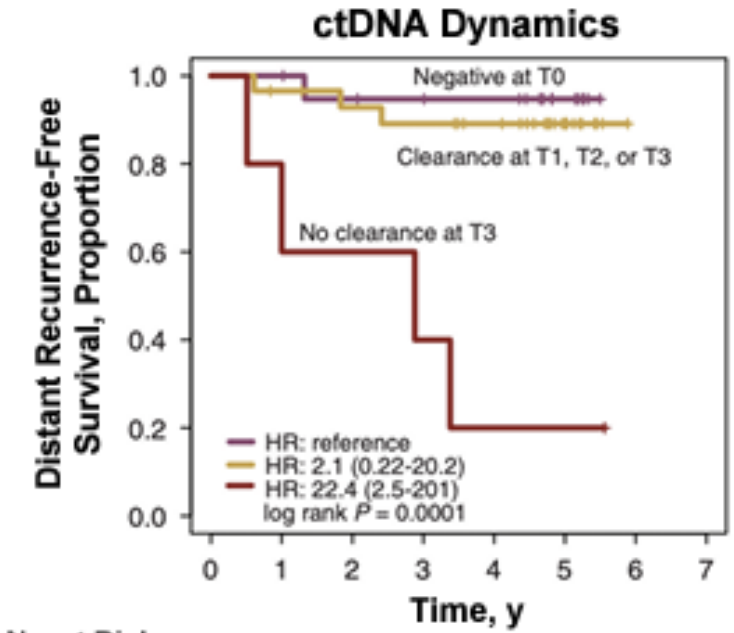


ctDNA[1]

ctdna

- The dynamics of **circulating tumor DNA (ctDNA)** in plasma can provide important prognostic information
- Patients with **persistence of detectable ctDNA** after (neo)adjuvant treatment have a **poor prognosis** and may warrant an escalation of treatment

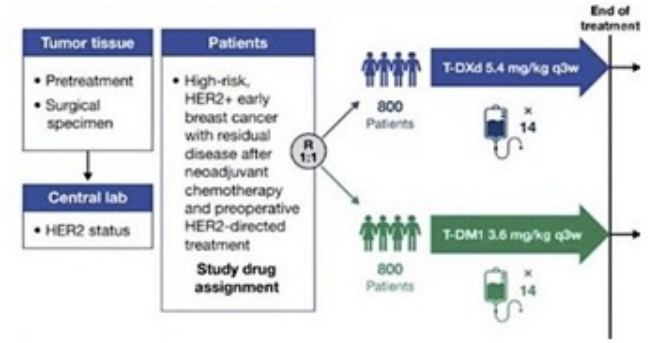




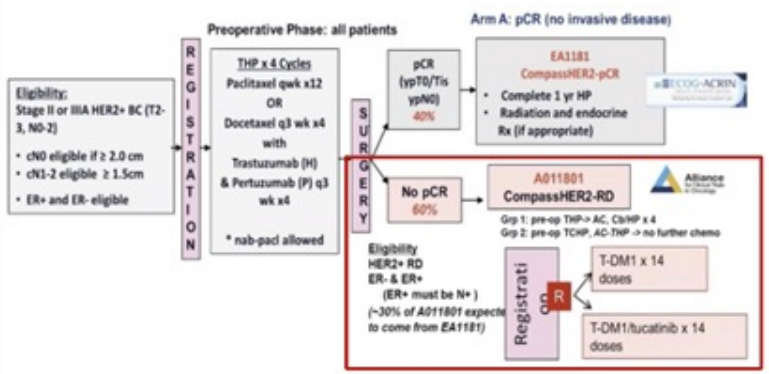
No. at Risk								
Groups								
Negative at T0	20	20	18	17	16	8	0	0
Clearance at T1, T2, or T3	29	27	25	24	21	12	0	0
No clearance at T3	5	4	3	2	1	1	0	0

Can We De-escalate Chemotherapy and potentially cure patients ?

DESTINY-Breast05: Substituting Post-Neoadjuvant T-DM1 with T-DXd



CompassHER2-RD: Adding Tucatinib to Post-Neoadjuvant T-DM1



Future Directions

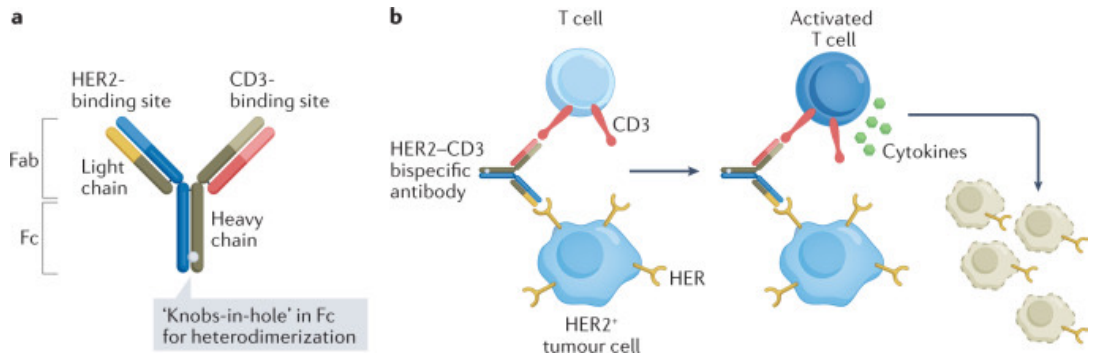


Table 1 | Select HER2-targeted antibody–drug conjugates in development

Drug name	Linker type	Payload	Payload MOA	DAR	Clinical trial ID	Clinical trial data	Reference
Trastuzumab duocarmycin	Cleavable	Duocarmycin (vc-seco-DUBA)	DNA alkylator	2.8	NCT04602117 (phase I), NCT03262935 (phase III)	Phase III trial SYD985 vs TPC: median PFS 7 vs 4.9 mo; HR 0.64, *P*=0.002	Saura Manich et al.[144]
Disitamab vedotin (RC48-ADC)	Cleavable	MMAE	Microtubule inhibitor	4	NCT02881190 (phase I), NCT03500380 (phase II), NCT04400695 (phase III)	Phase I trial in HER2+ cancers: ORR 15%; DCR 45%	Xu et al.[216]
A166	Cleavable	Duo-5	Microtubule inhibitor	2.8	CTR20181301 NCT03602079 (phase I)	Phase I trial in advanced solid tumours: ORR 59-71% based on the dose, DCR ~85%	Hu et al.[217]
ALT-P7	Cleavable	MMAE	Microtubule inhibitor	2	NCT03281824 (phase I)	Phase I trial in HER2+ MBC: DCR 72%, CBR 32%	Park et al.[218]
ARX788	Non-cleavable	AS269- synthetic dolastatin	Microtubule inhibitor	2	CTR20171162 (phase I), NCT04829604 (phase II)	Phase I trials in HER2+ MBC: ORR 66%; DCR 100%	Hurvitz et al.[219]
BB-1701	Cleavable	Eribulin	Microtubule inhibitor	4	NCT04257110 (phase I)	Not applicable	Not applicable
DB-1303	Cleavable	DXd derivative	Topoisomerase 1 inhibitor	8	NCT05150691 (phase I)	Not applicable	Not applicable
DX126-262	Unknown	Tubulysin	Microtubule inhibitor	NR	CTR20191224 (phase I)	Not applicable	Zhang et al.[220]
FS-1502/IKS014	Unknown	MMAE	Microtubule inhibitor	NR	NCT03944499 (phase I)	Not applicable	Fasching[221]
Zanidatamab zovodotin	Cleavable	Auristatin based	Microtubule inhibitor	2	NCT03821233 (phase I)	Phase I trial in advanced solid tumours. ORR 13%; DCR 50%; CBR 25%; MTD not reached	Jhaveri et al.[222]

CBR, clinical benefit rate; DAR, drug-to-antibody ratio; DCR, disease control rate; DXd, deruxtecan; HR, hazard ratio; MBC, metastatic breast cancer; MMAE, monomethyl auristatin E; MOA, mechanism of action; MTD, maximum tolerated dose; NR, not reported; ORR, overall response rate; PFS, progression-free survival; TPC, treatment of physician's choice.