GETTHI

Grupo Español de Oncología Transversal
y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 2: Novedades terapéuticas frente a dianas "clásicas"

18 de noviembre de 2021 - *Formato virtual*

Nuevos fármacos antiHER2 como diana transversal

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Familia HER

- Human Epidermal Receptors
- También llamada ErbB
- Fundamentales para el desarrollo y mantenimiento de muchos órganos
- 28 tipos de homo/heterodímeros
- Combinación con 11 factores de crecimiento → más de 600 complejos ligando-receptor
- Her 2 no tiene ligando específico y puede actuar como co- receptor

- Receptores de membrana protein tirosin kinasas:
  - Dominio extracelular
  - Dominio transmembrana
  - Dominio intracelular
- Her2 es resistente a la internalización y degradación
- 4 miembros:
  - HER1 (cromosoma 7)
  - HER2 (cromosoma 17)
  - HER3 (cromosoma 12)
  - HER4 (cromosoma 2)

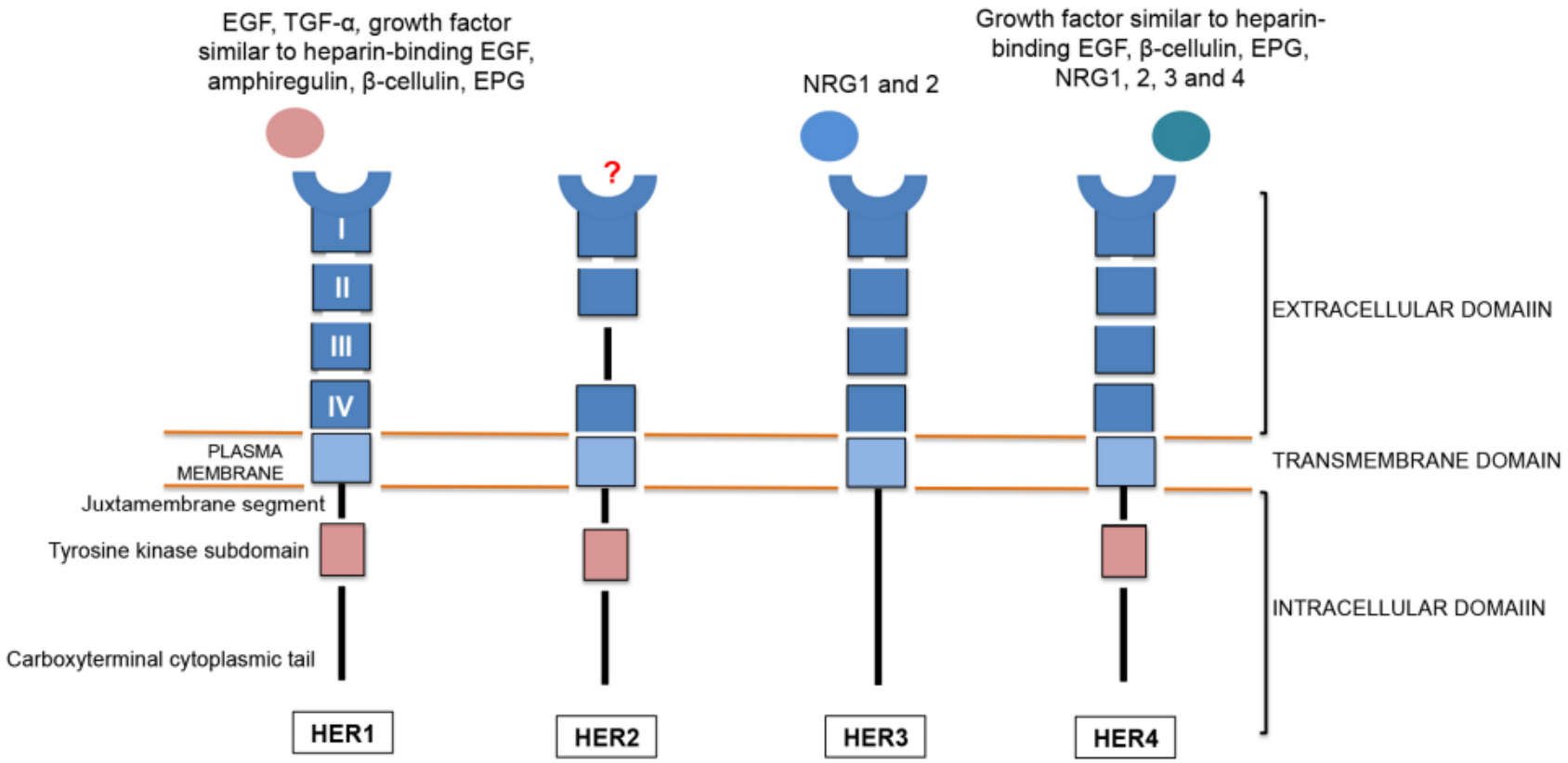
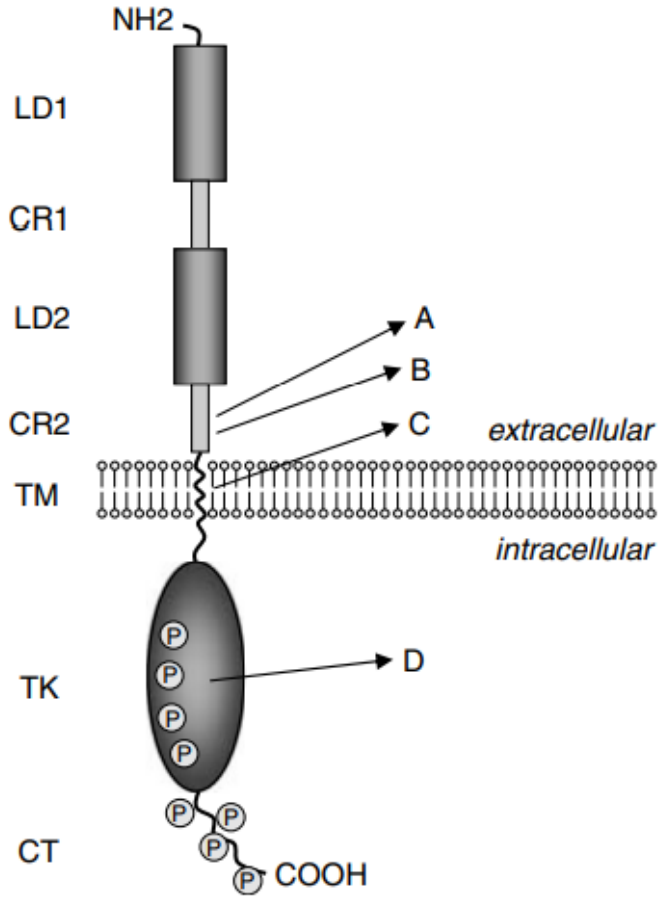


FIGURE 1 - General arrangement of receptors HER1/2/3/4 and their natural soluble ligands. The extracellular domain has four subdomains, and domains I and II are involved in binding the ligand. The carboxy-terminal tail contains tyrosine residues that can be phosphorylated. HER3 does not have a tyrosine kinase domain. To date, there are no known ligands for HER2. Epidermal growth factor (EGF), transforming growth factor alpha (TGF-α), amphiregulin, β-cellulin, growth factor similar to heparin-binding EGF, epiregulin (EPG) and neuregulin (NRG).

Braz. J. Pharm. Sci. 2017;53(2):e16076

HER2

- Implicado en la iniciación y progresión del cáncer
- Asociado a mal pronóstico y puede predecir la respuesta a hormonoterapia y quimioterapia
- El mecanismo más frecuente es la sobreexpresión de la proteína HER 2 por amplificación del gen HER2, seguido de mutaciones missense activadoras del gen Her2
- Suele ser un evento precoz en el desarrollo del cáncer



Oncogene (2007) 26, 6469–6487

Table 1. Rate of HER2 overexpression (immunohistochemistry), mutation (direct sequencing) and amplification (*in situ* hybridization) in the principal solid tumors.

Cancer	Mutation (%)	Overexpression (%)	Amplification (%)	HER2 positive (%)
Bladder	~4	23–80	0–32	–
Micropapillary carcinoma	–	–	15–42	–
Typical carcinoma	–	–	~9	–
Breast	~2	15–20	15–20	15–20
Colorectal	~5	–	5–20	5–43
Gastric plus gastroesophageal junction	~2	7–34	8–27	–
Diffuse type	–	–	–	2–6
Intestinal type	–	–	–	21–32
Mixed type	–	–	–	5–20
Lung	~2	11–32	2–23	–
Adenocarcinoma	–	–	–	29–35
Large cell carcinoma	–	–	–	0–20
Squamous cell carcinoma	–	–	–	1–18
Ovary	~1	9–37	5–27	–
Salivary gland	~0.5	–	–	–
Adenoid cystic carcinoma	–	–	–	7–56
Mucoepidermoid carcinoma	–	–	–	30–38
Terminal duct carcinoma	–	–	–	23–89

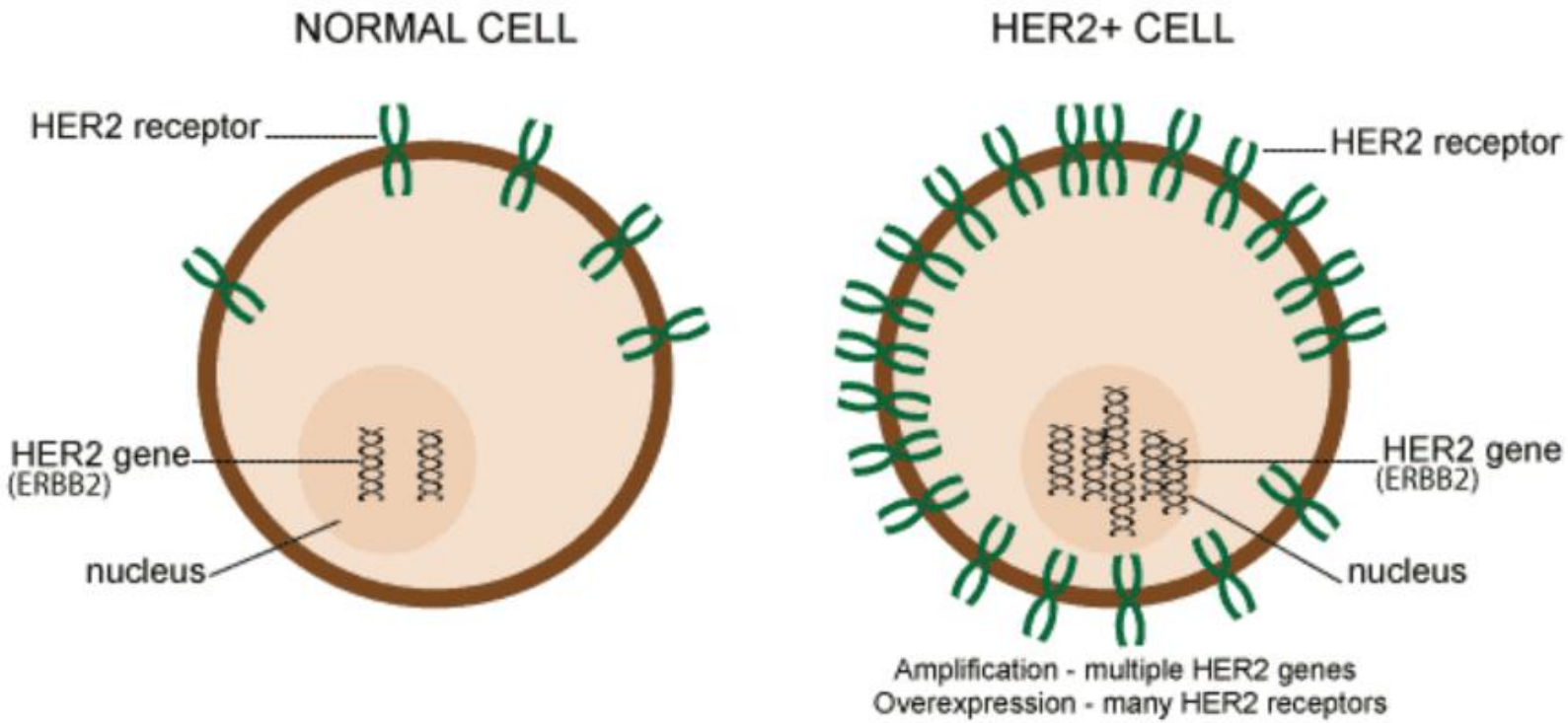
The wide range of frequencies of HER2 overexpression and *HER2* gene amplification is related to the different investigated cohorts and different criteria to assess HER2 status. For some cancers, frequencies of HER2 overexpression and/or *HER2* amplification were reported as pulled together as HER2 positive owing to the high correlation between HER2 protein status and *HER2* gene status. Mutational data taken from [10]; data of HER2 overexpression, amplification and positivity taken from [14–26].

Future Oncol. (2014) 10(8)

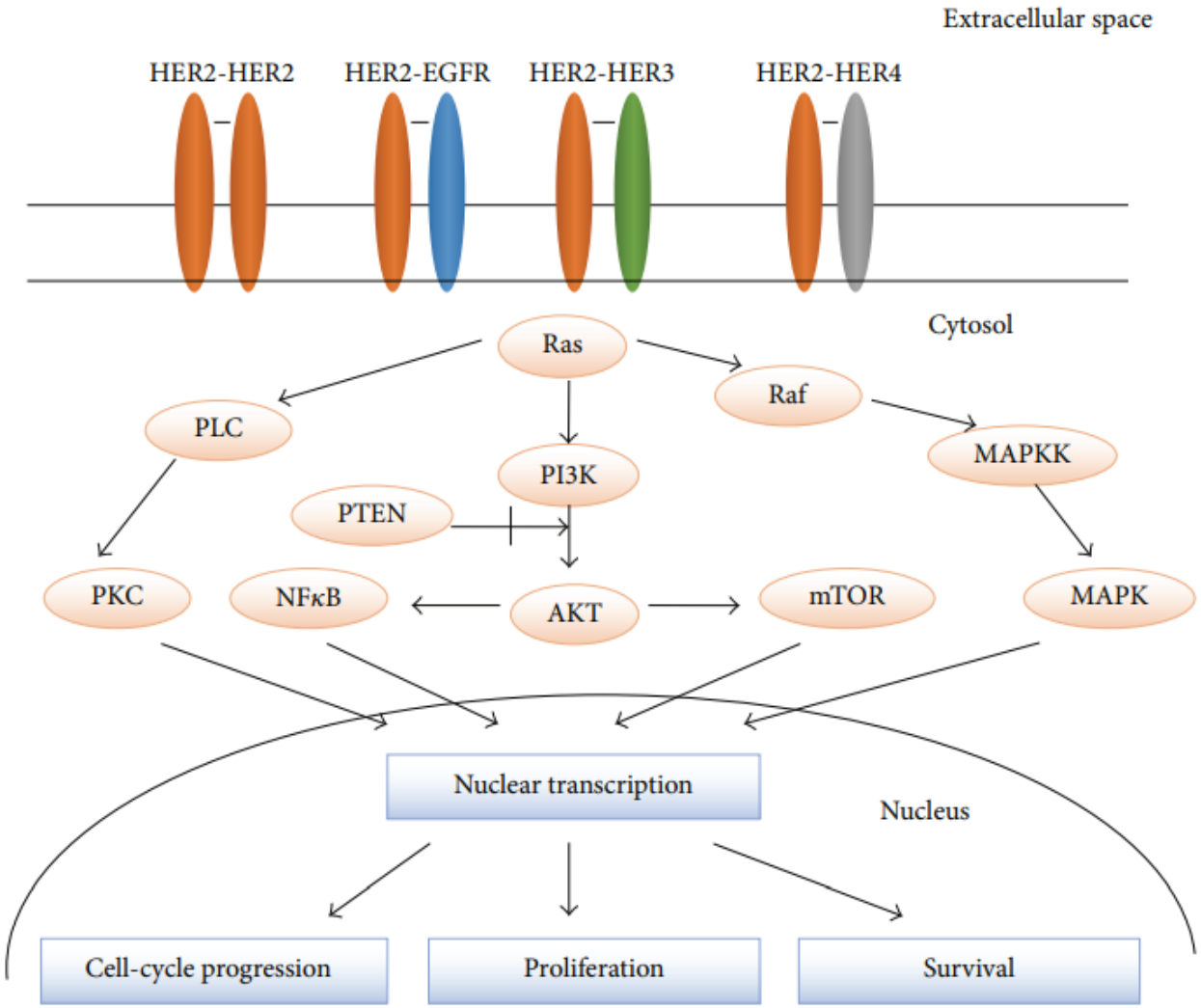
Table 2 Percentage of cases from studies deposited in cbioportal.org where HER2 alterations are found as well as data from US registries showing the number of deaths in the US per year from each associated cancer type

Cancer type	HER2 alterations (% cases)		Estimated annual deaths (US)	Estimated HER2 mutant deaths (US)
	Mutation	Amplification		
Colorectal (DFCI)	5.8	ND	50310	2918
Lung SCC	3.4	ND	72828	2476
Lung adenocarcinoma	2.6	2.6	72828	1894
Bladder (MSKCC)	11	1.8	15580	1714
Bladder (BGI)	10.1	ND	15580	1574
Colorectal (TCGA)	2.8	2.4	50310	1409
Breast (METABRIC)	2.8	15.1	40430	1132
Stomach	9.1	ND	10990	1000
Bladder (TCGA)	6.3	3.1	15580	982
Glioblastoma	7.7	ND	12000	924
Lung small cell	3.4	ND	24276	825
Breast (TCGA)	1.8	12.5	40430	728
Cutaneous SCC (metastatic)	17.2	ND	3270	562
Oesophagus	3.3	12	15450	510
Stomach (TCGA)	4.2–4.6	12.5–13.7	10990	462–506
Gallbladder	9.4	ND	3630	341
Head and neck SCC	3.1	ND	8390	260
Endometrial	3.3	8.3	7181	237
Cholangiocarcinoma	5.7	ND	3630	207
Cervical SCC	5.2	3.1	3417	178
Uterine carcinosarcoma	9.1	ND	1407	128
Low grade glioma	3.3	ND	2500	83
Prostate neuroendocrine	19.6	1.9	Rare	Rare
Bladder (plasmacytoid)	15.2	3	Rare	Rare

Connell CM, Doherty GJ. *ESMO Open* 2017;**2**:e000279. doi:10.1136/esmoopen-2017-000279



https://www.whathealth.com/breastcancer/her2receptor.html



http://dx.doi.org/10.1155/2014/852748

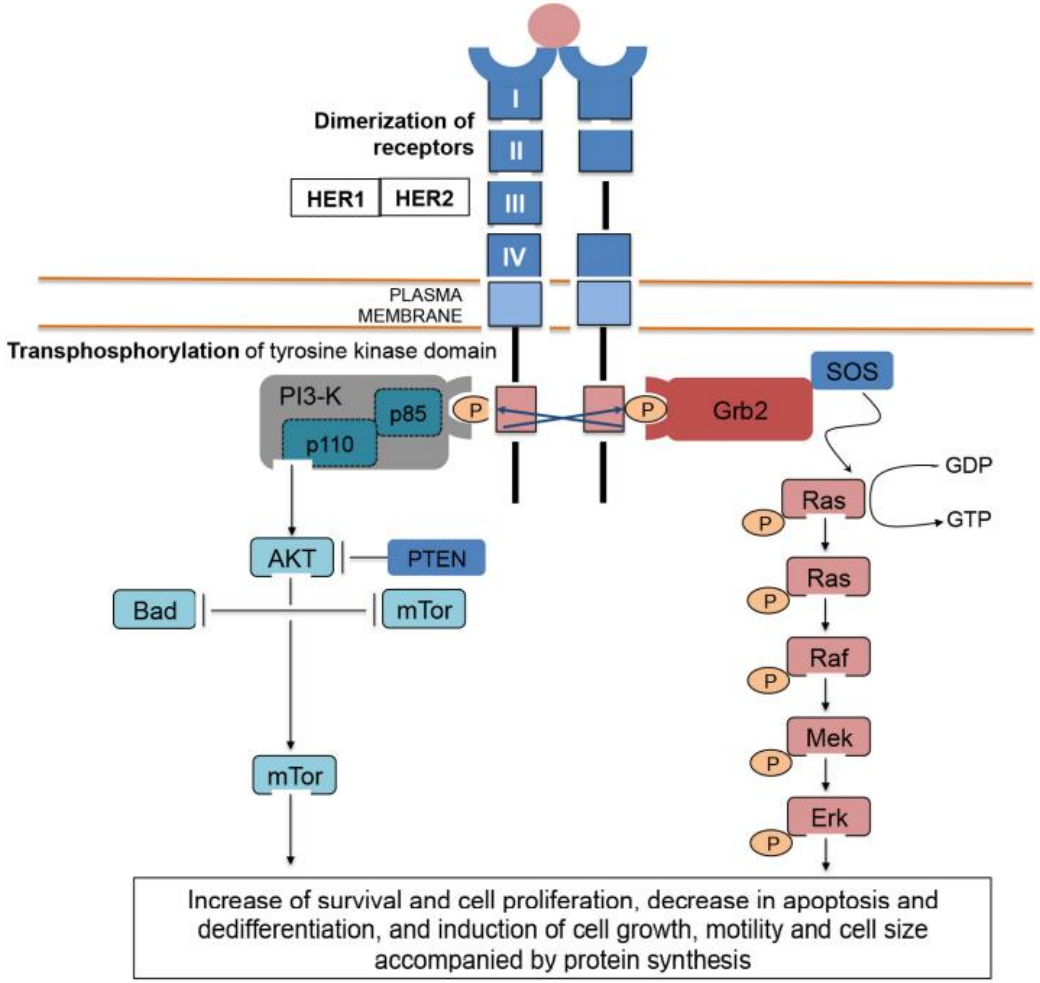


FIGURE 2 - Activation of the cytoplasmic signaling pathways Ras/Raf/MEK/Erk1-2 and phosphatidylinositol 3-kinase (PI3-K/AKT) following dimerization of human epidermal receptors (e.g., HER1/HER2 heterodimer) resulting from recognition of the receptor extracellular domain by ligands.

Braz. J. Pharm. Sci. 2017;53(2):e16076

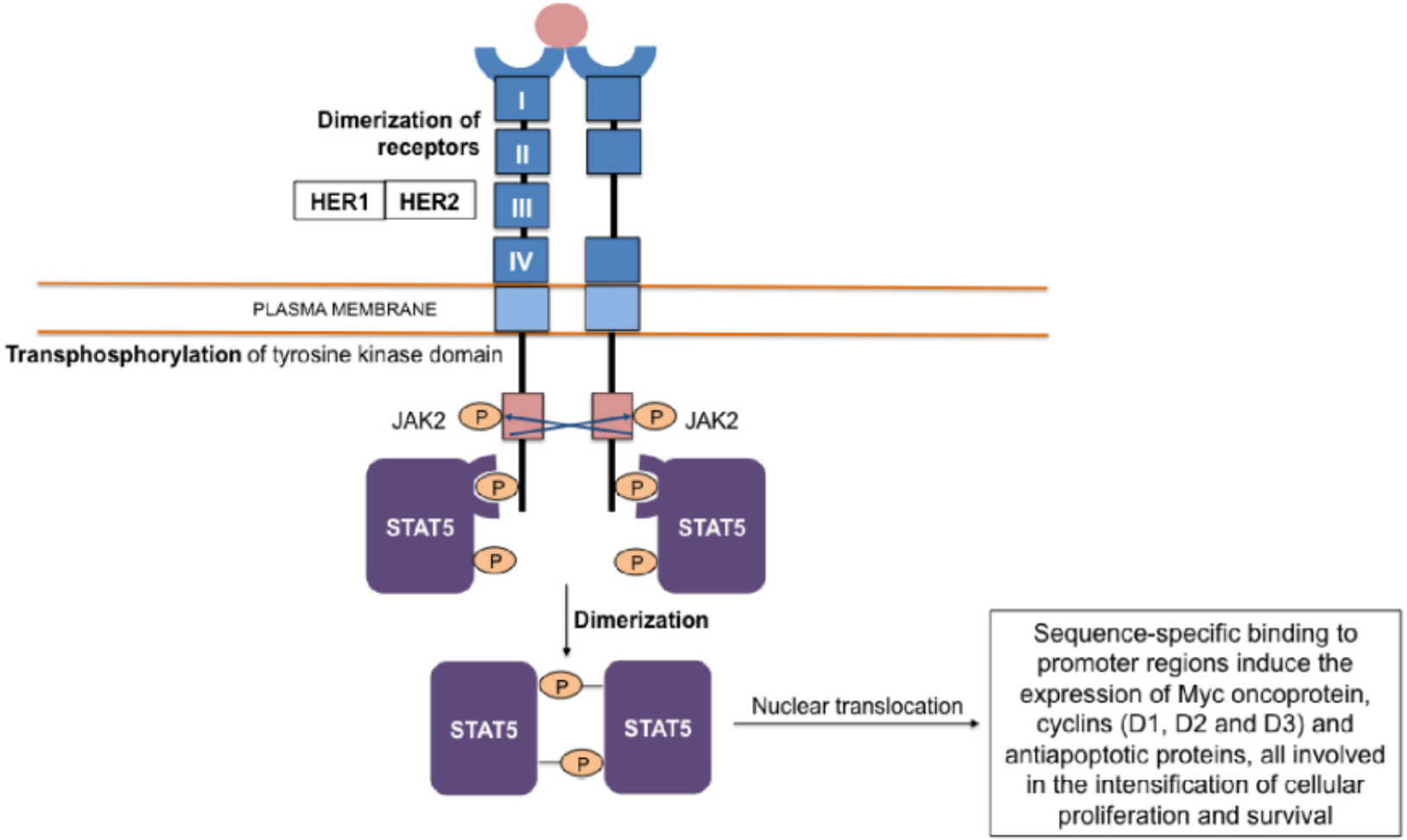
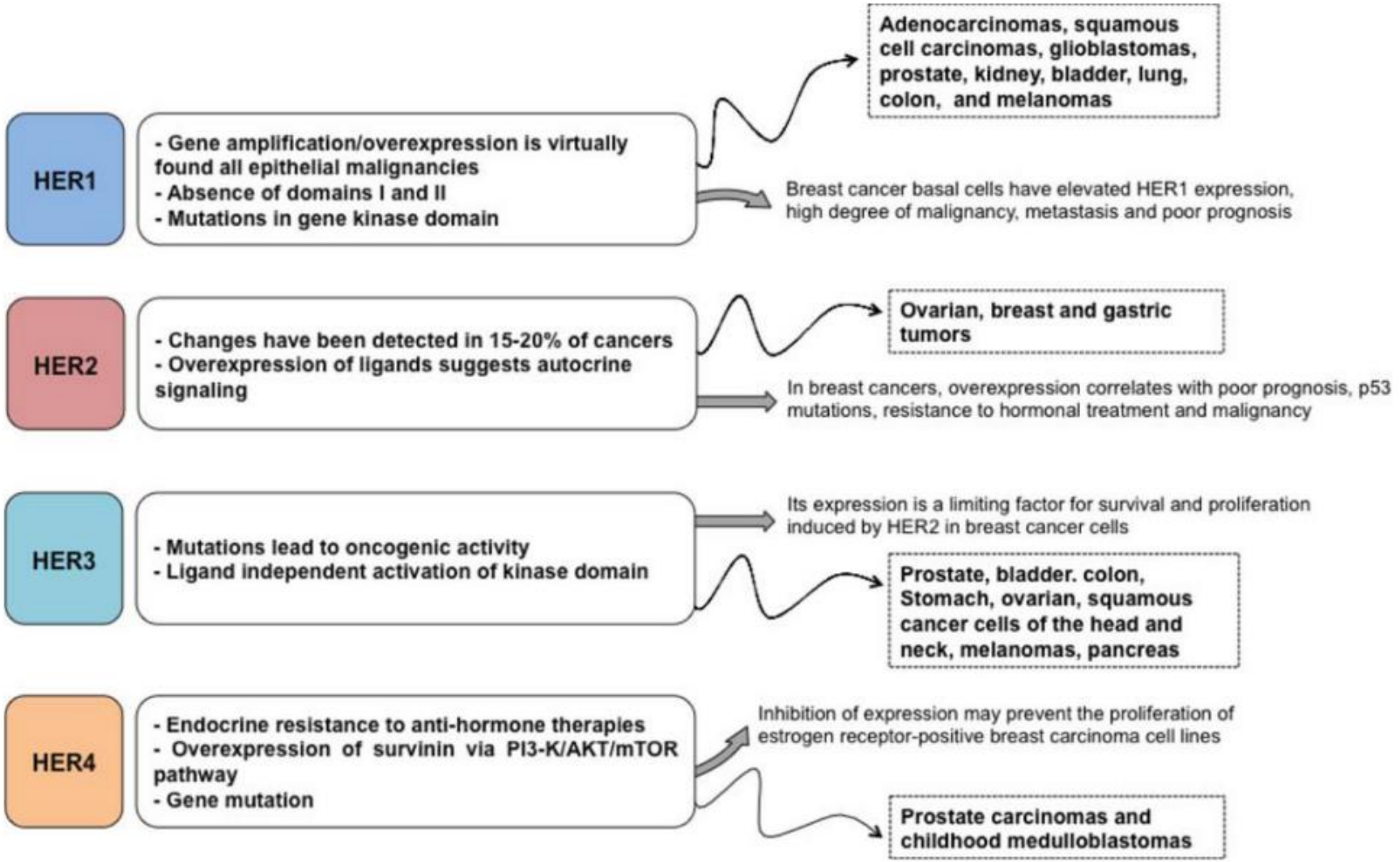


FIGURE 3 - Signaling activation of JAK/STAT pathway by human epidermal receptors (HER). STAT-STAT dimerization may occur between identical or different dimers (e.g., STAT1/STAT2 or STAT5/STAT5).

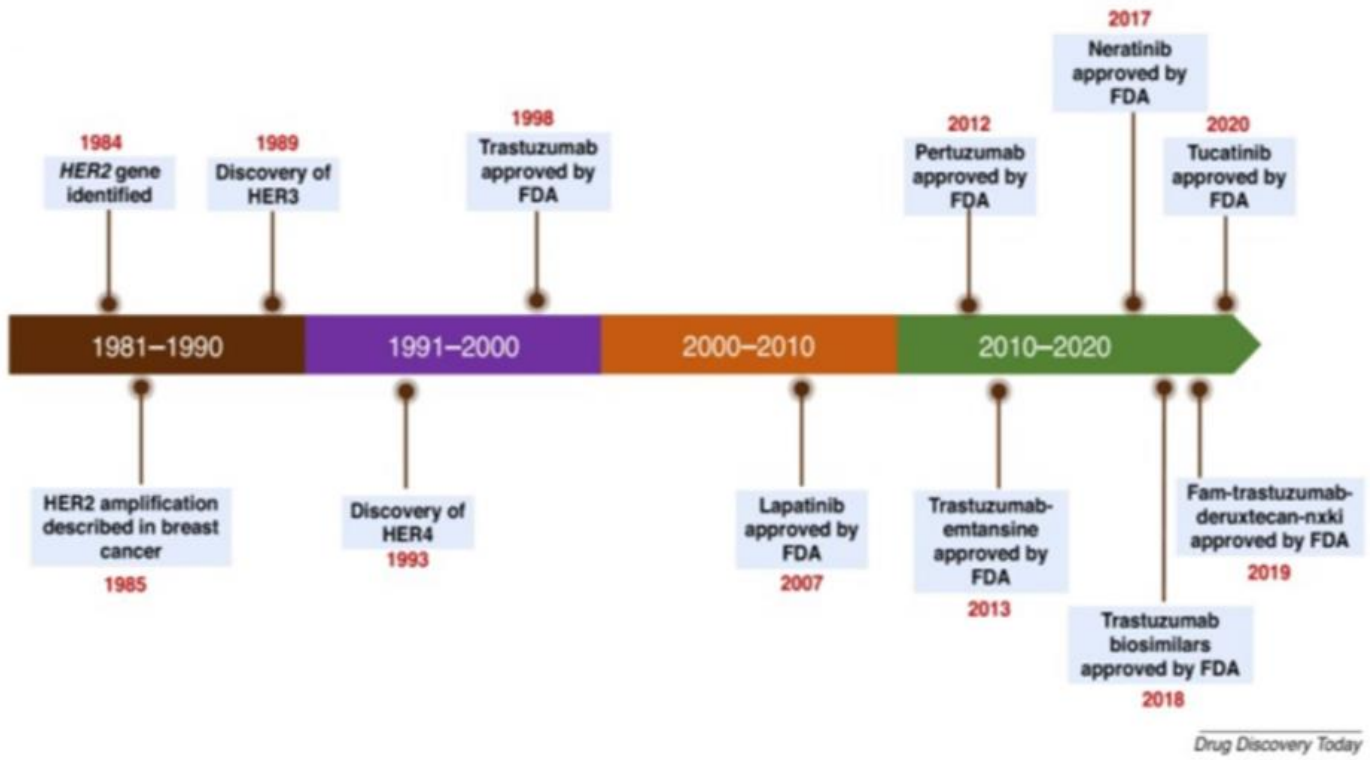
Braz. J. Pharm. Sci. 2017;53(2):e16076



Braz. J. Pharm. Sci. 2017;53(2):e16076

FIGURE 4 - Most common alterations in human epidermal receptors to induce malignancy and development of resistance.

ASCO Meeting Library



Fármacos anti Her2

- Inhibidores tirosin kinasa
  - Lapatinib
  - Neratinib
  - Tucatinib
- Anticuerpos monoclonales
  - Trastuzumab
  - Pertuzumab
- Conjugados anticuerpo-droga
  - Trastuzumab emtansina
  - Trastuzumab deruxtecan

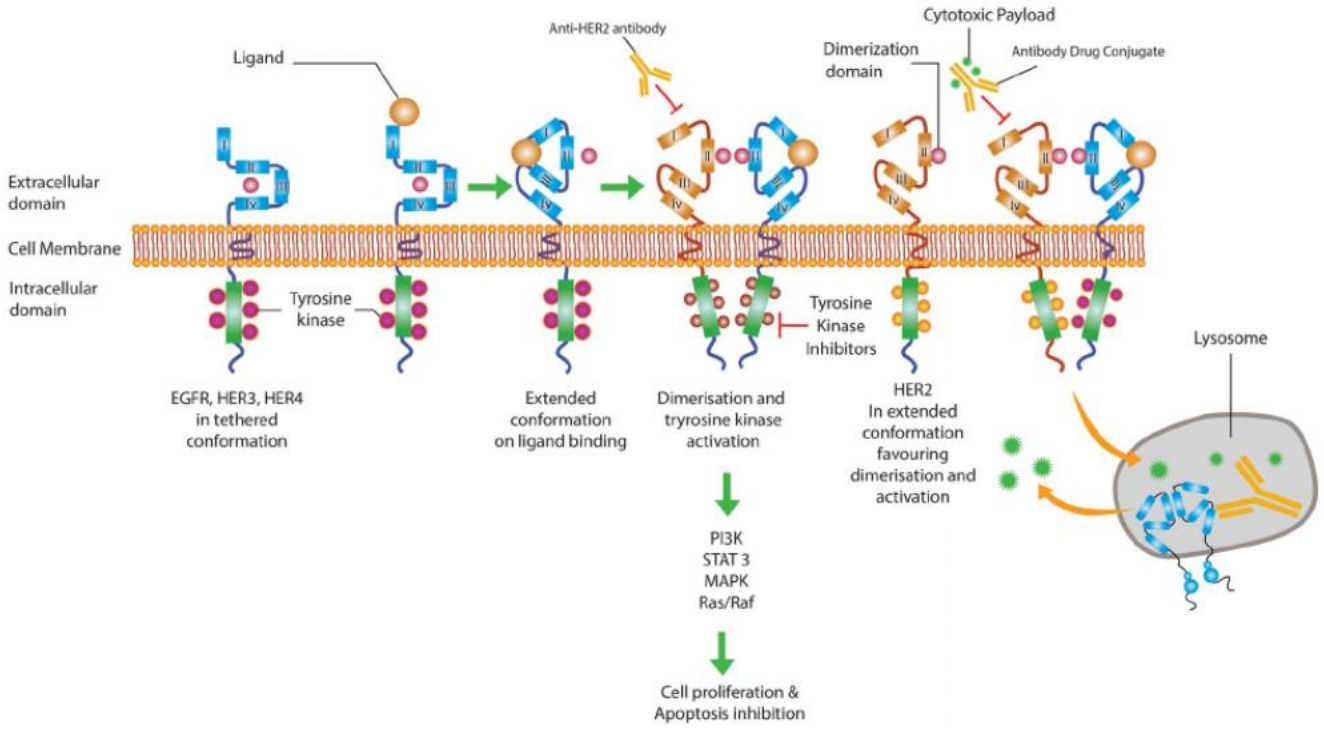
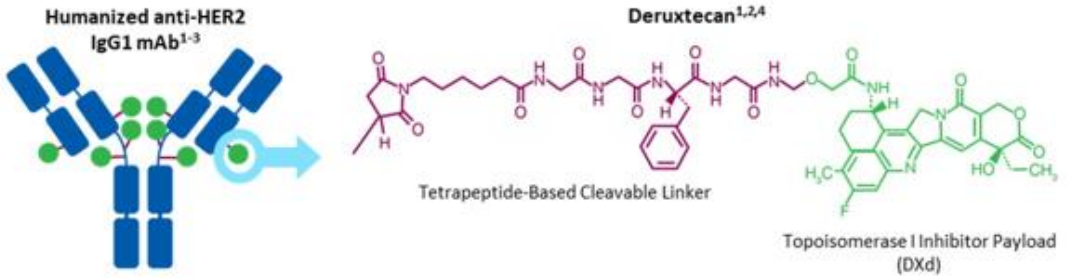


TABLE 1. Overview of the anti-HER2 agents that have been approved in breast and gastric cancers

Anti-HER2 agent	Structure	Mechanism of action	Approved indications#
Trastuzumab	Monoclonal antibody	Immune-mediated response causing internalization and downregulation of HER2	HER2+ breast cancer HER+ gastric cancer
Pertuzumab	Monoclonal antibody	Prevents HER2-HER3 dimerization (combined with trastuzumab and docetaxel)	HER2+ breast cancer
Trastuzumab emtansine (ado-trastuzumab emtansine)	Antibody-drug conjugate (ADC)	Trastuzumab and DM1 (cytotoxic maytansinoid); DM1 binds microtubules and inhibits cell division in the tumor cells	HER2+ breast cancer
Trastuzumab deruxtecan (DS-8201)	Antibody-drug conjugate (ADC)	Trastuzumab and a topoisomerase I inhibitor conjugate deruxtecan	HER2+ breast cancer*
Lapatinib	Dual tyrosine kinase inhibitor	Blocks EGFR/HER2 protein kinase activity	ER+/EGFR+/HER2+ breast cancer
Neratinib	Dual tyrosine kinase inhibitor	Blocks EGFR/HER2 activity by covalently binding with a cysteine side chain in those receptors	HER2+ breast cancer
Tucatinib	Tyrosine kinase inhibitor	Highly selective inhibitor of the kinase domain of HER2 receptor	HER2+ breast cancer**

Bosn J Basic Med Sci. 2021;21(1):1-4

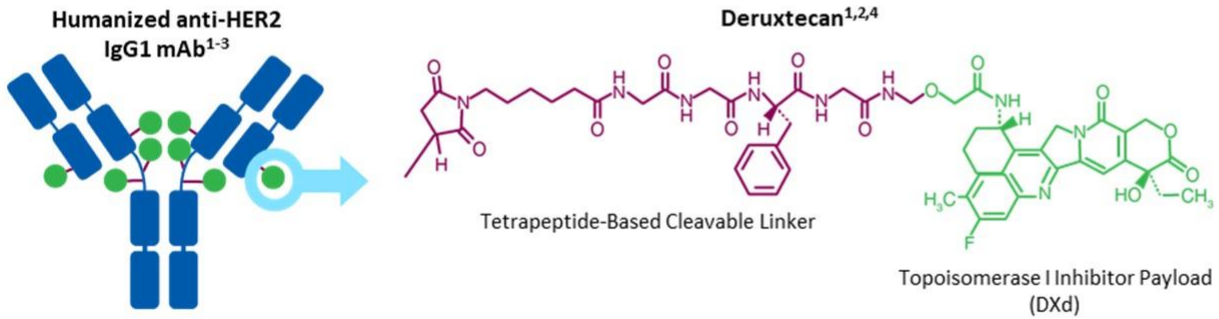


Trastuzumab deruxtecan

T-DXd is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

Presented By Egbert Smit at TBD

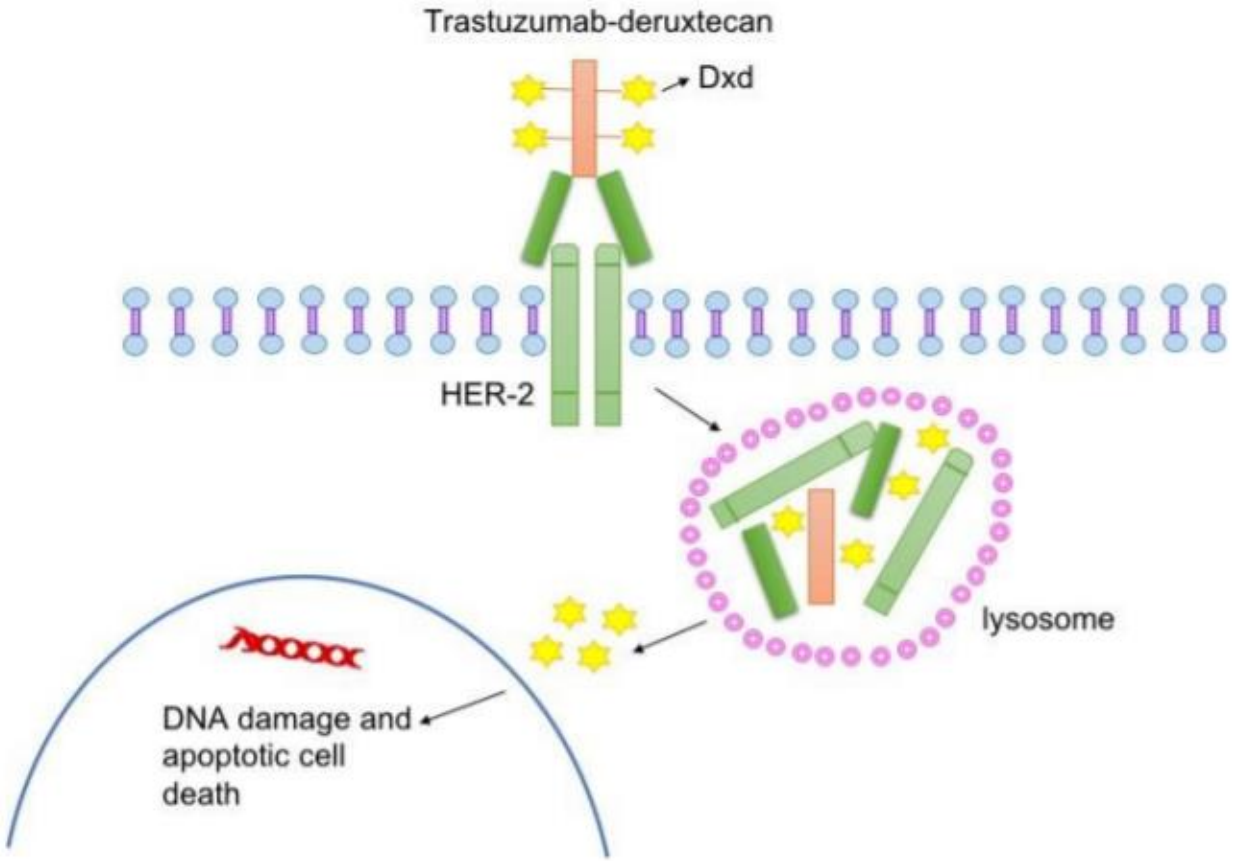


Figure 1. Mechanism of action of trastuzumab deruxtecan (T-DXd): following binding to HER2 on tumor cells, T-DXd undergoes internalization and intracellular linker cleavage by lysosomal ezymes. Upon release, the membrane permeable DXd enters the nucleus and causes DNA damage and apoptotic cell death.

Int. J. Mol. Sci. **2021**, 22, 4774

Table 1. Summary of the main results of clinical trials of T-DXd.

Trial Name, NCT Number	Type of Study	Condition(s)	Sample Size	Median Follow Up	ORR	DCR	mDOR	mPFS	mOS
DS8201-A-J101, NCT02564900	Phase 1	HER2-positive mBC pretreated with T-DM1	$n = 115$	9.9 mo	59.5%	93.7%	20.7 mo	22.1 mo	NR
		HER2-low mBC refractory to standard therapies	$n = 54$	NA	37%	87%	10.4 mo	11.1 mo	29.4 mo
		HER2-positive mGC/GEJC pretreated with ≥2 therapies, including TTZ	$n = 44$	5.5 mo	43.2%	79.5%	7.0 mo	5.6 mo	12.8 mo
		HER2-positive metastatic solid tumors [1]	$n = 22$	9.5 mo	27.3%	81.8%	NR	11.0 mo	23.4 mo
		HER2-expressing or mutated metastatic NSCLC	$n = 18$	11.0 mo	55.6%	83.3%	9.9 mo	11.3 mo	NR
		HER2-expressing metastatic CRC	$n = 20$	3.0 mo	5%	80%	7.4 mo	4 mo	15.6 mo
DESTINY-Breast01, NCT03248492	Phase 2	HER2-positive mBC pretreated with ≥2 anti-HER2 agents	$n = 184$	11.0 mo	60.9%	97.3%	14.8 mo	16.4 mo	NR
DESTINY-Gastric01, NCT03329690	Phase 2, randomized	HER2-positive mGC/GEJC pretreated with ≥2 therapies, including TTZ	$n = 125$	NA	42.9%	85.7%	11.3 mo	5.6 mo	12.5 mo
DESTINY-Lung01, NCT03505710 *	Phase 2	HER2-expressing or mutated metastatic NSCLC	$n = 42$	8.0 mo	61.9%	90.5%	NR	14.0 mo	NA
DESTINY-CRC01, NCT03384940 *	Phase 2	HER2-expressing metastatic CRC	$n = 78$ [2]	NA	45.3%	83%	NR	6.9 mo	NR

* Preliminary results (ongoing clinical trials). [1] Patients in this cohort included: $n = 8$ salivary gland tumors; $n = 2$ breast cancers (1 HER2 low and 1 HER2 status missing per central laboratory assessment); $n = 2$ esophageal cancers; $n = 2$ endometrial cancers; $n = 2$ Paget disease; $n = 2$ biliary tract cancer; $n = 1$ pancreatic cancer, $n = 1$ uterine cervix carcinoma, $n = 1$ extraskeletal myxoid chondrosarcoma, and $n = 1$ small-intestine adenocarcinoma. [2] Response and survival results are reported for the cohort of patients with HER2 positive (IHC 3+) tumors ($n = 53$). Abbreviations: CI, confidence interval; CRC, colorectal cancer; GEJC, gastroesophageal junction cancer; DCR, disease control rate; DOR, duration of response; IHC, immunohistochemistry; mBC, metastatic breast cancer; mGC, metastatic gastric cancer; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; T-DM1, trastuzumab emtansine; TTZ, trastuzumab.

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

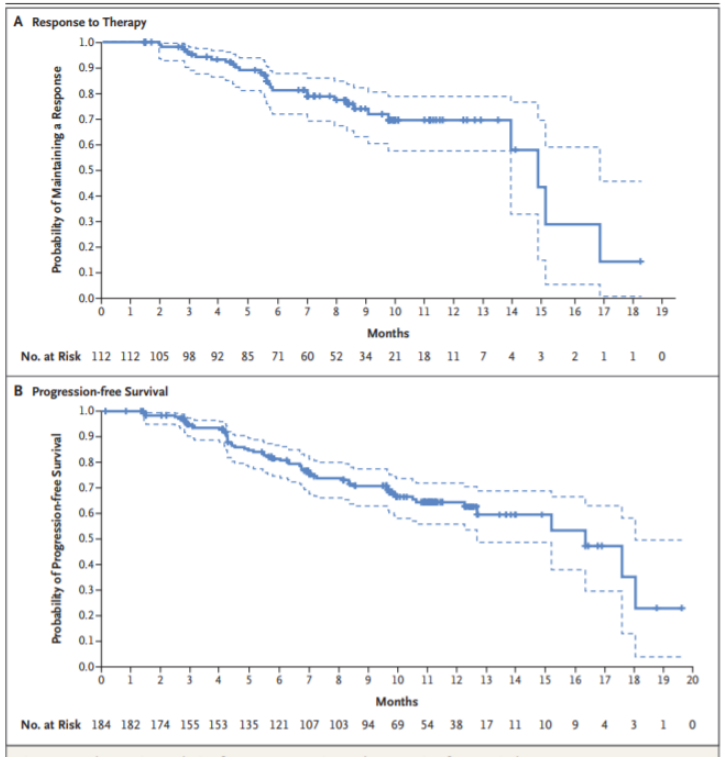


Table 2. Adverse Events in the Overall Population of 184 Patients.*

Adverse Events	Any Grade	Grade 3	Grade 4
	number of patients (percent)		
Any adverse event†	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count‡	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia§	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased white-cell count¶	39 (21.2)	11 (6.0)	1 (0.5)
Decreased platelet count‖	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain**	31 (16.8)	2 (1.1)	0
Decreased lymphocyte count††	26 (14.1)	11 (6.0)	1 (0.5)
Adverse events of special interest			
Interstitial lung disease‡‡	25 (13.6)	1 (0.5)	0
Prolonged QT interval	9 (4.9)	2 (1.1)	0
Infusion-related reaction	4 (2.2)	0	0
Decreased left ventricular ejection fraction§§	3 (1.6)	1 (0.5)¶¶	0

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*

Table 3. Adverse Events Occurring in at Least 20% of the Patients Treated with Trastuzumab Deruxtecan.*

Preferred Term	Trastuzumab Deruxtecan (N=125)			Physician's Choice of Chemotherapy (N=62)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased†	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anemia‡	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased§	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White-cell count decreased¶	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (8)	0	0
Constipation	30 (24)	0	0	14 (23)	0	0
Pyrexia	30 (24)	0	0	10 (16)	0	0
Alopecia	28 (22)	0	0	9 (15)	0	0
Fatigue	27 (22)	9 (7)	0	15 (24)	2 (3)	0
Lymphocyte count decreased‖	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

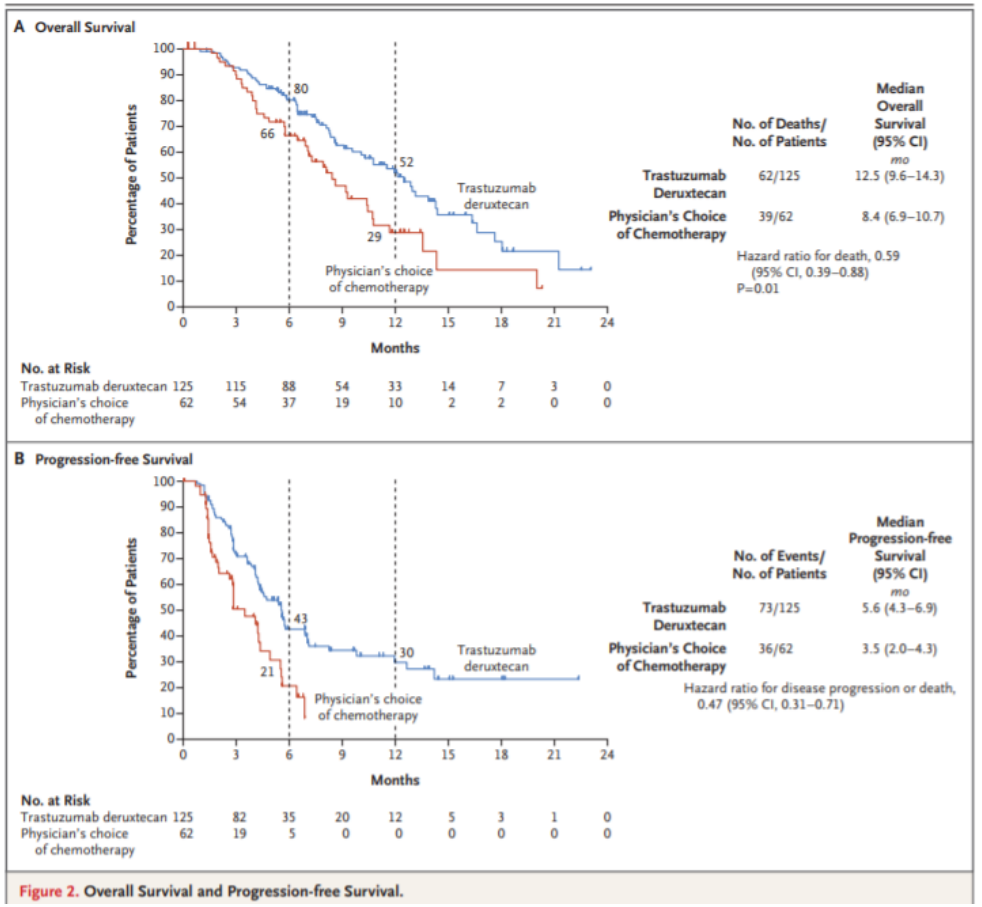


Figure 2. Overall Survival and Progression-free Survival.

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)

Patients

- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- RAS/BRAF wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

T-DXd 6.4 mg/kg q3w

Cohort A (n = 53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

A futility monitoring was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C

Cohort B (n = 7)
HER2 IHC 2+/ISH−

Cohort C (n = 18)
HER2 IHC 1+

Primary endpoint

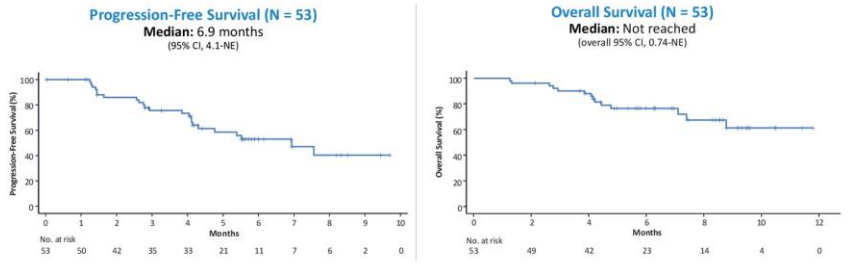
- Confirmed ORR by independent central review (ICR) in Cohort A

Data cutoff: August 9, 2019

- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

DESTINY-CRC01 Cohort A

Progression-Free and Overall Survival



Median follow-up for OS was 5.4 month (range, 1.2-11.8 months).

DESTINY-Lung01 Study Design

An open-label, multicenter, phase 2 study (NCT03505710)

Patients

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- HER2-expressing *or* HER2-activating mutation[a]
- No prior HER2-targeted therapy, except pan-HER TKIs

Cohort 1 (n = 42)
HER2 expressing (IHC 3+ or IHC 2+)

Cohort 2 (n = 42)
HER2 mutated

T-DXd 6.4 mg/kg q3w

Primary endpoint

- Confirmed ORR by independent central review

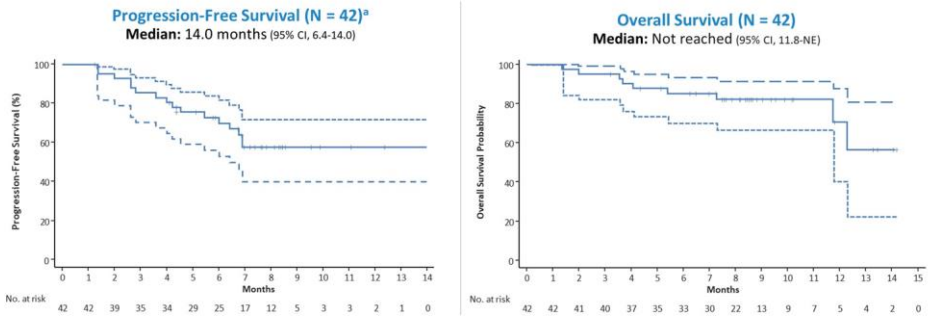
Data cutoff: November 25, 2019

- 45.2% of patients (19/42) in Cohort 2 remained on treatment
- 54.8% discontinued, primarily for progressive disease and adverse events (21.4% each)

[a] Based on local assessment of archival tissue.

DESTINY-Lung01 HER2-Mutated NSCLC

Progression-Free and Overall Survival



[a] Patients were censored if they discontinued treatment; the median is estimated by Kaplan-Meier analysis. Median follow-up, 8.0 months (range, 1.4-14.2 months). Dashed lines indicate upper and lower 95% CI.

Table 2. Overview of the main ongoing clinical trials of T-DXd in solid tumors (source: clinicaltrials.gov; and rctportal.niph.go.jp; accessed: 16 March 2021).

Trial Name, NCT Number	Type of Study	Condition(s)	Drug(s)	Estimated Sample Size	Primary Endpoint(s)
Breast cancer					
DESTINY-Breast02, NCT03523585	Phase 3, randomized	HER2-positive metastatic BC, progressed on prior TDM-1	T-DXd Investigator's choice CT (TTZ/lapatinib + capecitabine)	$n = 600$	PFS by BICR
DESTINY-Breast03, NCT03529110	Phase 3, randomized	HER2-positive metastatic BC, progressed on prior TTZ + taxane	T-DXd T-DM1	$n = 500$	PFS by BICR
DESTINY-Breast04, NCT03734029	Phase 3, randomized	HER2-low metastatic BC, progressed on prior CT	T-DXd Investigator's choice CT	$n = 540$	PFS by BICR
DESTINY-Breast05, NCT04622319	Phase 3, randomized	HER2-positive primary BC who do not achieve CR after neoadjuvant therapy	T-DXd T-DM1	$n = 1600$	IDFS
DESTINY-Breast06, NCT04494425	Phase 3, randomized	HER2-low HR-positive metastatic BC	T-DXd Investigator's choice CT	$n = 850$	PFS
DESTINY-Breast07, NCT04538742	Phase 1b/2, randomized	HER2-positive metastatic BC, in second or later lines of treatment	T-DXd monotherapy or in combination [1]	$n = 350$	AEs and SAEs frequency
DESTINY-Breast08, NCT04556773	Phase 1b	HER2-low metastatic BC	T-DXd + capecitabine/durvalumab+paclitaxel/ capivasertib/anastrozole/fulvestrant	$n = 185$	AEs and SAEs frequency
HER2CLIMB-04, NCT04539938	Phase 2, single arm	HER2- positive metastatic BC, progressed on ≥2 prior anti-HER2-based regimens	T-DXd + tucatinib	$n = 70$	ORR
NCT04553770	Phase 2, randomized	HER2-low HR-positive early stage BC	T-DXd +/− anastrozole	$n = 88$	pCR rate
DEBBRAH, NCT04420598	Phase 2, single arm, multicohort	HER2-positive or HER2-low BC with CNS disease	T-DXd	$n = 39$	PFS, CNS ORR, OS
BEGONIA, NCT03742102	Phase 1b/2	Triple negative BC	durvalumab + T-DXd vs. durvalumab + other anti-cancer agents [2]	$n = 170$	AEs, ORR

Table 2. *Cont.*

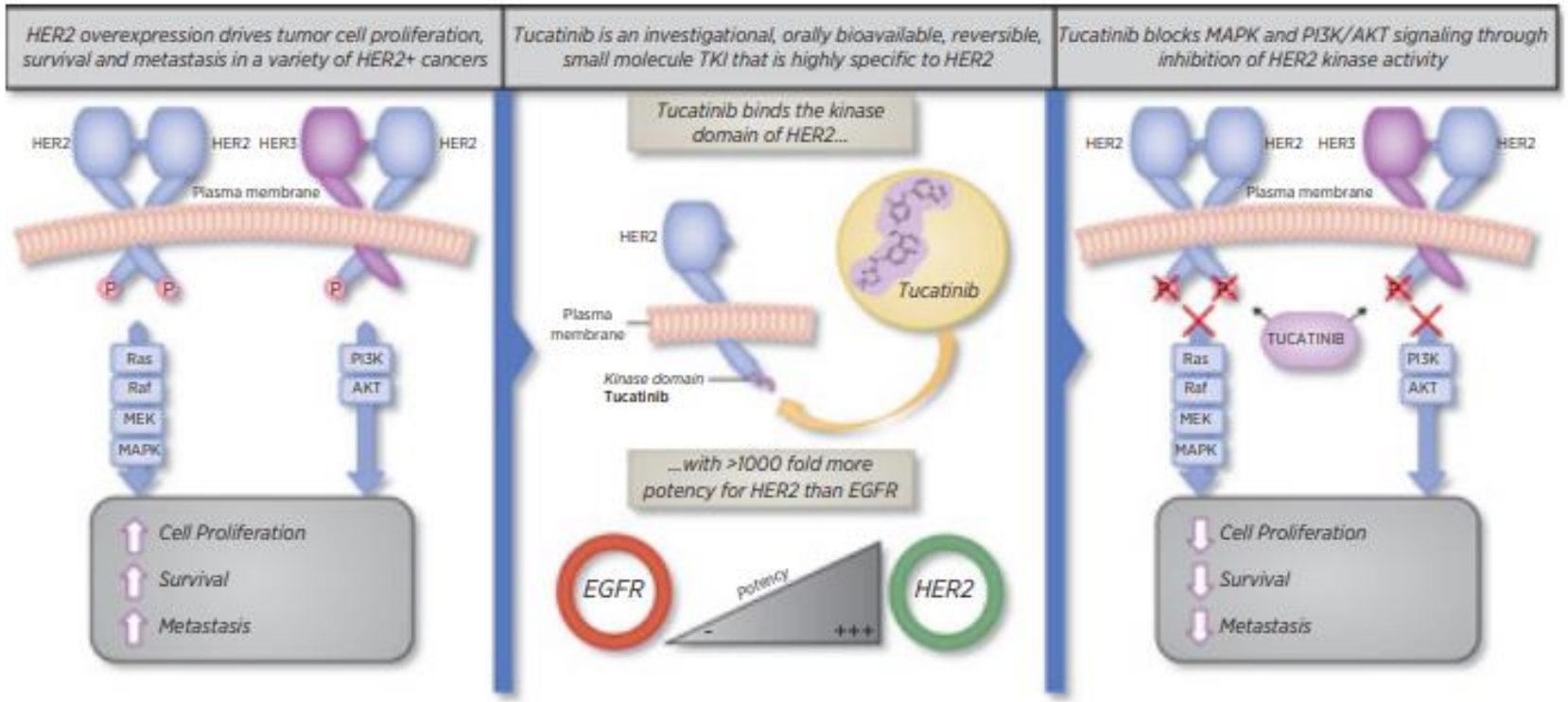
Trial Name, NCT Number	Type of Study	Condition(s)	Drug(s)	Estimated Sample Size	Primary Endpoint(s)
Gastric cancer					
DESTINY-Gastric02, NCT04014075	Phase 2, single arm	HER2-positive gastric cancer, progressed on prior TTZ	T-DXd	$n = 74$	ORR by BICR
DESTINY-Gastric03, NCT04379596	Phase 1b/2, randomized	HER2-positive gastric cancer, progressed on prior TTZ	T-DXd monotherapy or in combination [3] TTZ, 5FU/capecitabine + cisplatin/oxaliplatin	$n = 220$	AEs and SAEs frequency, ORR
NSCLC					
DESTINY-Lung01, NCT03505710	Phase 2, single arm	HER2-expressing or mutated NSCLC	T-DXd	$n = 170$	ORR by BICR
DESTINY-Lung02, NCT04644237	Phase 2, randomized	HER2-mutated metastatic NSCLC	T-DXd 6.4 mg/kg q3w T-DXd 5.4 mg/kg q3w	$n = 150$	ORR by BICR
DESTINY-Lung03, NCT04686305	Phase 1b	HER2-positive treatment naive non-squamous NSCLC	T-DXd + durvalumab +/−CDDP/CBDCA or pemetrexed	$n = 120$	AEs and SAEs frequency
HUDSON, NCT03334617	Phase 2, biomarker directed, umbrella study	NSCLC, progressed on prior anti-PD1/PD-L1 therapy	durvalumab + T-DXd vs. durvalumab + other novel anti-cancer agents [4]	$n = 410$	ORR
Miscellaneous					
DESTINY-CRC01, NCT03384940	Phase 2	HER2-expressing colorectal cancer, progressed on ≥2 prior lines of CT	T-DXd	$n = 90$	ORR
NCT04616560	Phase 2, single arm	Newly diagnosed or recurrent HER2-positive osteosarcoma [5]	T-DXd	$n = 77$	% of event-free patients at 24 weeks
DESTINY-PanTumor01, NCT04639219	Phase 2, single arm	HER2-expressing metastatic solid tumors	T-DXd	$n = 100$	ORR by BICR

Table 2. *Cont.*

Trial Name, NCT Number	Type of Study	Condition(s)	Drug(s)	Estimated Sample Size	Primary Endpoint(s)
		Miscellaneous			
DESTINY-PanTumor02, NCT04482309	Phase 2, single arm	HER2-expressing metastatic solid tumors [6]	T-DXd	$n = 280$	ORR
HERB, JMA-IIA00423	Phase 2, single arm	HER2-expressing biliary tract cancer	T-DXd	$n = 32$	ORR
NCT03523572	Phase 1b	HER2-expressing BC, urothelial cancer	T-DXd + nivolumab	$n = 99$	AEs frequency, ORR
NCT04585958	Phase 1	Uterine serous carcinoma, HER2-positive or -expressing solid tumors	T-DXd + olaparib	$n = 51$	MTD, AEs frequency
NCT04042701	Phase 1b	HER2-positive BC, HER2-expressing or mutated NSCLC	T-DXd + pembrolizumab	$n = 115$	MTD, ORR

[1] Combination therapies include: durvalumab, pertuzumab, paclitaxel, durvalumab and paclitaxel. [2] Anti-cancer agents include paclitaxel monotherapy, or in combination with capivasertib, or oleclumab. [3] Combination therapies include: 5FU, capecitabine, durvalumab, 5FU/capecitabine + oxaliplatin, 5FU/capecitabine + durvalumab. [4] Novel anti-cancer agents include: olaparib, AZD9150, AZD6738, vistusertib (AZD2014), oleclumab, cediranib, ceralasertib. [5] Patients with confirmed HER2 expression of >10% of tumor cells are eligible for enrolment in this trial. [6] This trial includes 7 tumor-specific cohorts: urothelial bladder cancer, biliary tract cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and rare tumors. Abbreviations: AEs, adverse events; BC, breast cancer; BICR, blinded independent central review; CBDCA, carboplatin; CDDP, cisplatin; CNS, central nervous system; CR, complete response; CT, chemotherapy; HR, hormone receptors; IDFS, invasive disease-free survival; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; pCR, pathologic complete response; PFS, progression-free survival; q3w, once every 3 weeks; SAEs, serious adverse events; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTZ, trastuzumab; 5-FU, 5-fluorouracile.

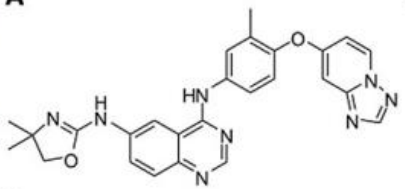
Tucatinib



Mol Cancer Ther; 19(4) April 2020

Figure 1.
Enzymatic and kinase screening assays reveal tucatinib potency and selectivity for HER2. **A,** Chemical structure of tucatinib. **B,** Calculated IC_{50} values for tucatinib, lapatinib, and neratinib in a kinase assay using recombinant HER2 and EGFR. **C,** Tucatinib inhibitory activity across a screen of 223 kinases, represented on a kinome dendrogram. Large circles represent kinases inhibited ≥ 50% at 1 μmol/L tucatinib, medium circles represent kinases inhibited ≥ 50% at 10 μmol/L tucatinib, and small circles represent kinases that did not reach 50% inhibition at 10 μmol/L. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

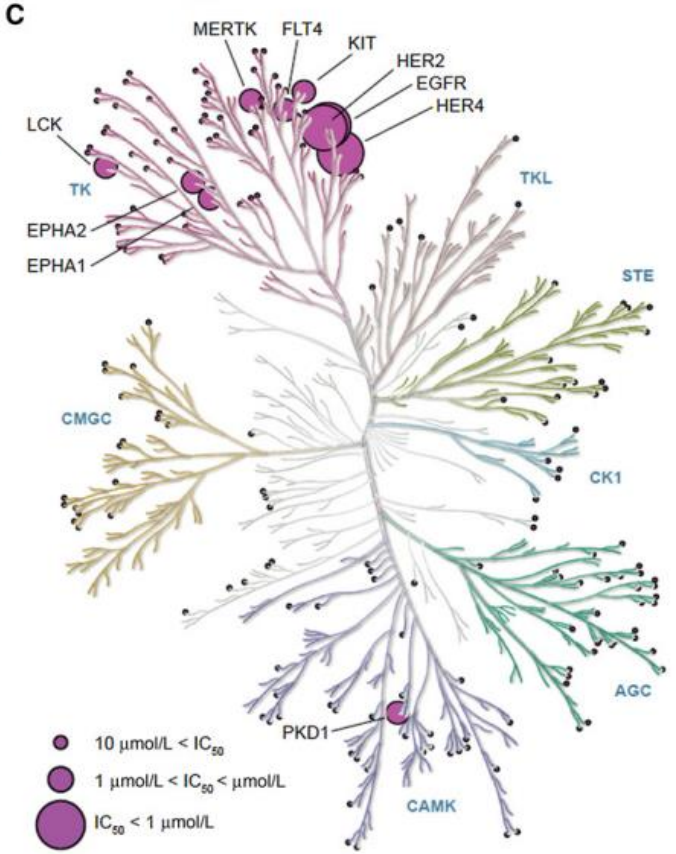
A



B

	HER2 IC_{50} (nmol/L)	EGFR IC_{50} (nmol/L)
Tucatinib	6.9	449
Lapatinib	109	48
Neratinib	5.6	1.8

C



Mol Cancer Ther; 19(4) April 2020

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

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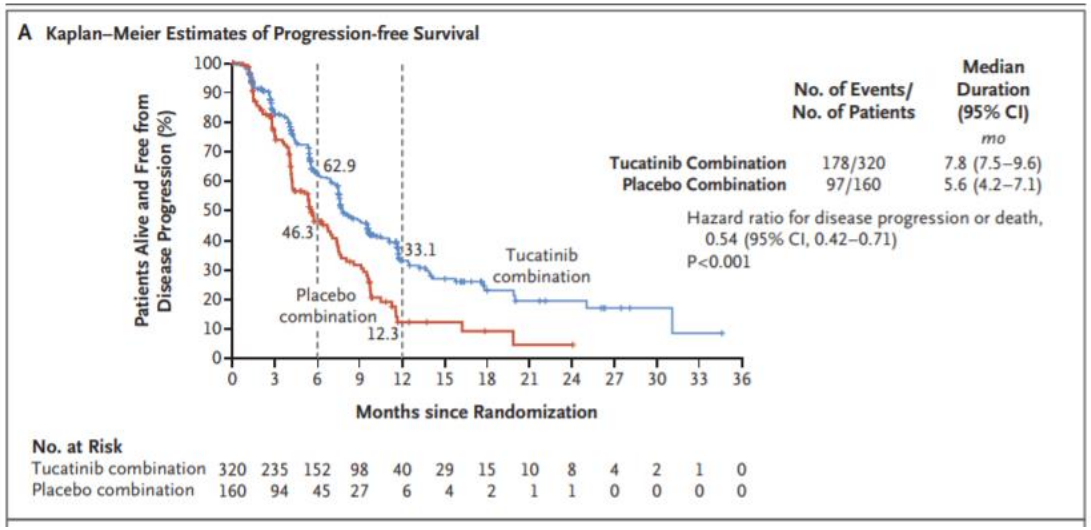

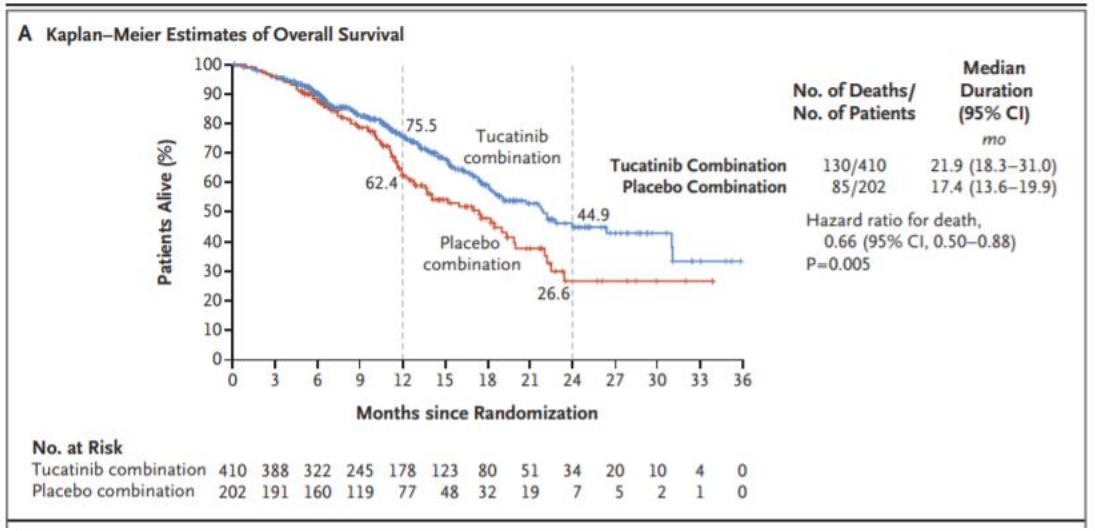

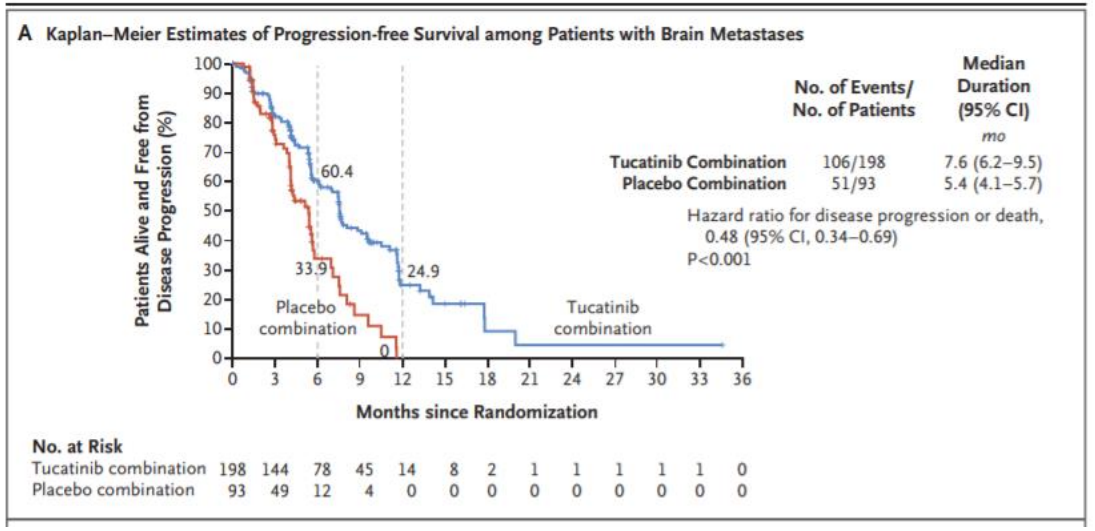

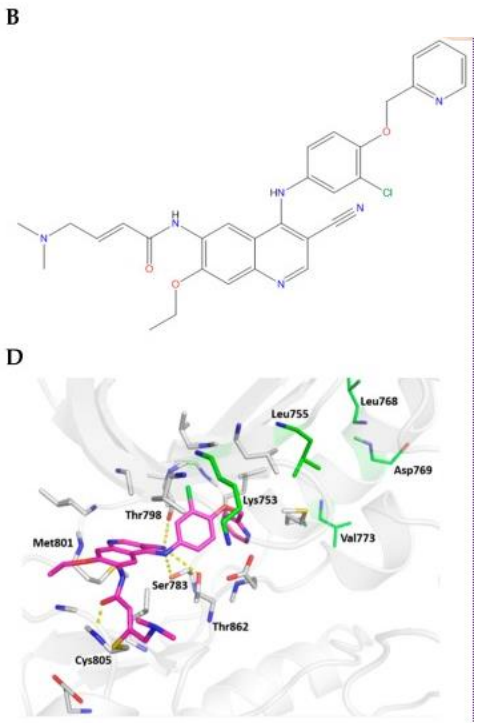

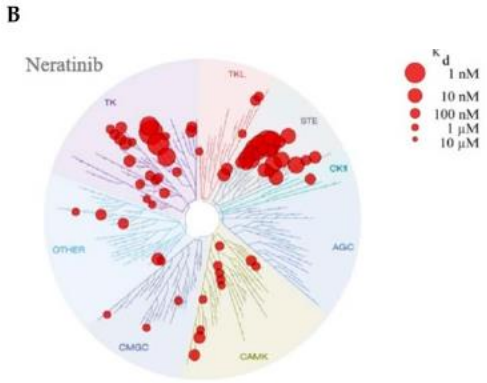

Neratinib

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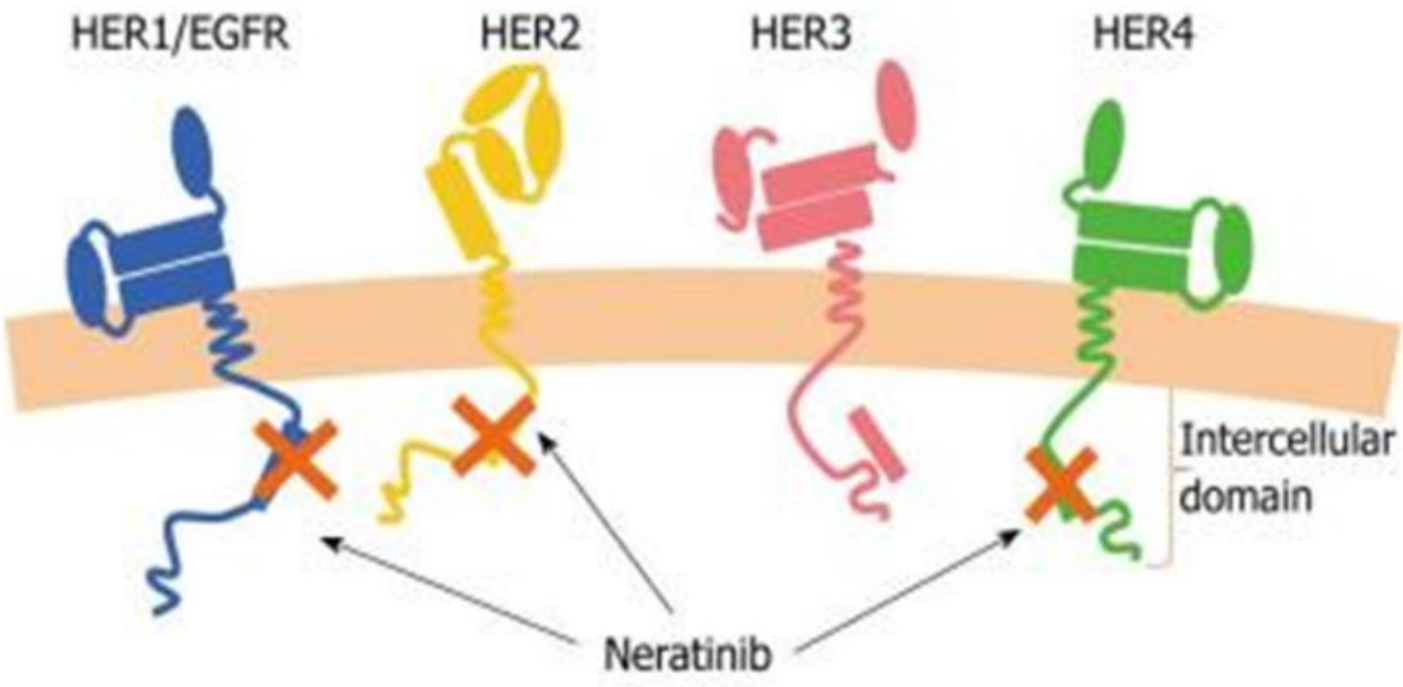

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Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial

Cristina Saura, MD[1]; Mafalda Oliveira, MD, PhD[1]; Yin-Hsun Feng, MD, PhD[2]; Ming-Shen Dai, MD, PhD[2]; Shang-Wen Chen, MD[2]; Sara A. Hurvitz, MD[3]; Sung-Bae Kim, MD, PhD[4]; Beverly Moy, MD, PhD[5]; Suzette Delaloge, MD, MSc[6]; William Gradishar, MD[7]; Norikazu Masuda, MD, PhD[8]; Marketa Palacova, MD[9]; Maureen E. Trudeau, MD[10]; Johanna Mattson, MD, PhD[11]; Yoon Sim Yap, MBBS[12]; Ming-Feng Hou, MD[13]; Michelino De Laurentiis, MD, PhD[14]; Yu-Min Yeh, MD[15]; Hong-Tai Chang, MD[16]; Thomas Yau, MBBS, MD[17]; Hans Wildiers, MD, PhD[18,19]; Barbara Haley, MD[20]; Daniele Fagnani, MD[21]; Yen-Shen Lu, MD, PhD[22]; John Crown, MBBCh, MD[23]; Johnson Lin, MD[24]; Masato Takahashi, MD, PhD[25]; Toshimi Takano, MD[26]; Miki Yamaguchi, MD, PhD[27]; Takaaki Fujii, MD, PhD[28]; Bin Yao, MS[29]; Judith Bebchuk, ScD[29]; Kiana Keyvanjah, PharmD[29]; Richard Bryce, MBChB[29]; and Adam Brufsky, MD, PhD[30]; for the NALA Investigators

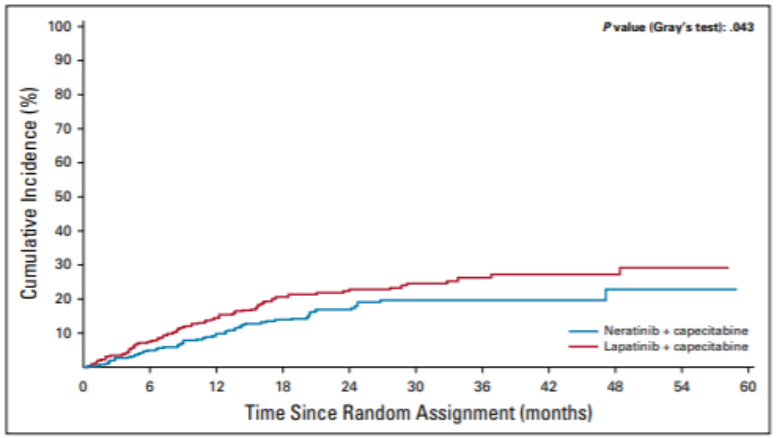

FIG 3. Intervention for CNS disease.

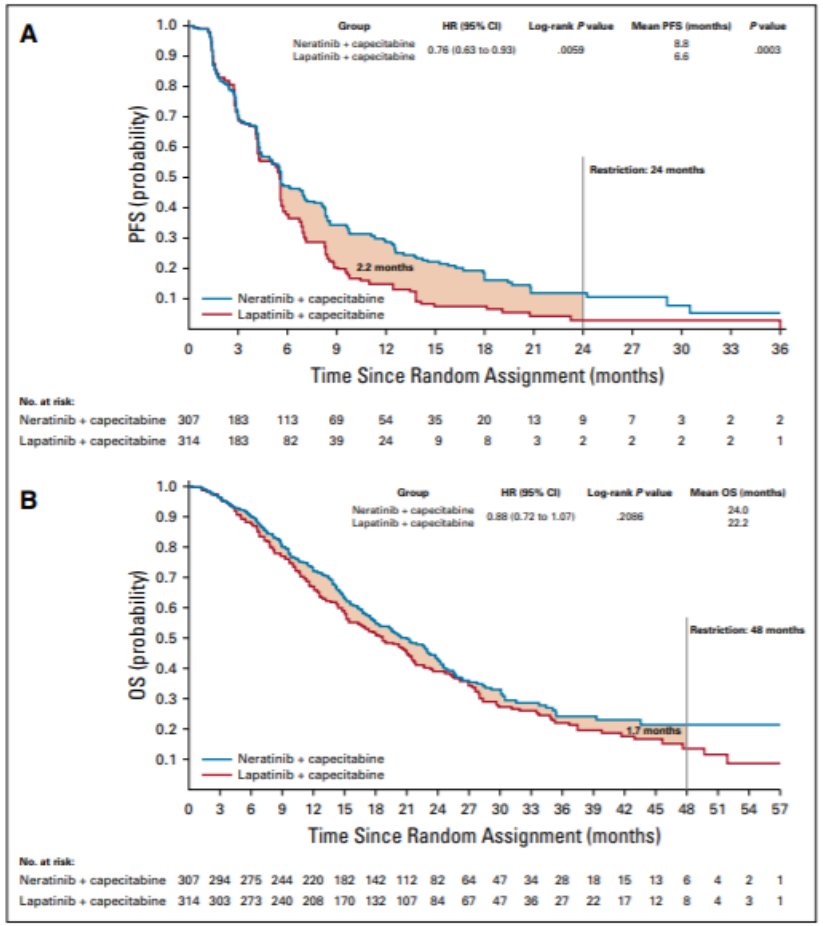

FIG 2. Kaplan-Meier curves for (A) centrally assessed progression-free survival (PFS), and (B) overall survival (OS) in the intention-to-treat population.

Toxicidades a vigilar

- Trastuzumab deruxtecan
  - Neumonitis/Enfermedad pulmonar intersticial
  - Neutropenia
  - Disminución FEVI
- Tucatinib
  - Toxicidad gastrointestinal
  - Elevación transaminasas
- Neratinib
  - Diarrea
  - Hepatotoxicidad

Table 3. Adverse Events Occurring in at Least 20% of the Patients Treated with Trastuzumab Deruxtecan.*

Preferred Term	Trastuzumab Deruxtecan (N=125)			Physician's Choice of Chemotherapy (N=62)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased†	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anemia‡	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased§	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White-cell count decreased¶	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (8)	0	0
Constipation	30 (24)	0	0	14 (23)	0	0
Pyrexia	30 (24)	0	0	10 (16)	0	0
Alopecia	28 (22)	0	0	9 (15)	0	0
Fatigue	27 (22)	9 (7)	0	15 (24)	2 (3)	0
Lymphocyte count decreased‖	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

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Table 2. Most Common Adverse Events.*

Event	Tucatinib-Combination Group (N=404)		Placebo-Combination Group (N=197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

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TABLE 3. Treatment-Emergent AEs Occurring in ≥ 10% of Patients in the Safety Population

	N+C (n = 303)		L+C (n = 311)	
AE	**All Grade**	**Grade 3/4**	**All Grade**	**Grade 3/4**
Diarrhea	252 (83.2)	74 (24.4)	206 (66.2)	39 (12.5)
Nausea	161 (53.1)	13 (4.3)	132 (42.4)	9 (2.9)
PPE syndrome	139 (45.9)	29 (9.6)	175 (56.3)	35 (11.3)
Vomiting	138 (45.5)	12 (4.0)	97 (31.2)	6 (1.9)
Decreased appetite	107 (35.3)	8 (2.6)	67 (21.5)	7 (2.3)
Fatigue	104 (34.3)	9 (3.0)	97 (31.2)	10 (3.2)
Constipation	94 (31.0)	4 (1.3)	41 (13.2)	1 (0.3)
Stomatitis	62 (20.5)	6 (2.0)	83 (26.7)	8 (2.6)
Weight decreased	60 (19.8)	1 (0.3)	41 (13.2)	2 (0.6)
Rash	30 (9.9)	0	69 (22.2)	2 (0.6)
Anemia	45 (14.9)	6 (2.0)	51 (16.4)	11 (3.5)
Dizziness	43 (14.2)	1 (0.3)	31 (10.0)	2 (0.6)
Cough	37 (12.2)	0	34 (10.9)	0
Abdominal pain	36 (11.9)	3 (1.0)	45 (14.5)	6 (1.9)
Asthenia	36 (11.9)	8 (2.6)	36 (11.6)	5 (1.6)
Hypokalemia	35 (11.6)	14 (4.6)	44 (14.1)	20 (6.4)
Paronychia	35 (11.6)	2 (0.7)	49 (15.8)	3 (1.0)
Pyrexia	33 (10.9)	0	32 (10.3)	1 (0.3)
Headache	32 (10.6)	1 (0.3)	51 (16.4)	3 (1.0)

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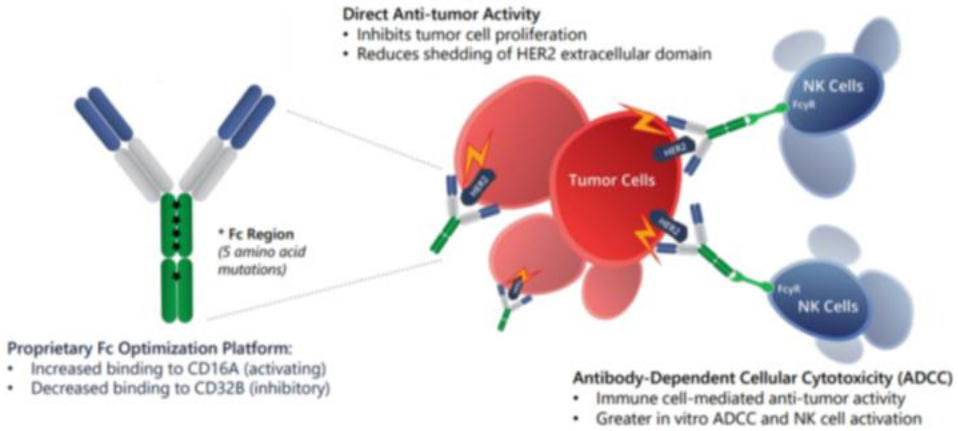
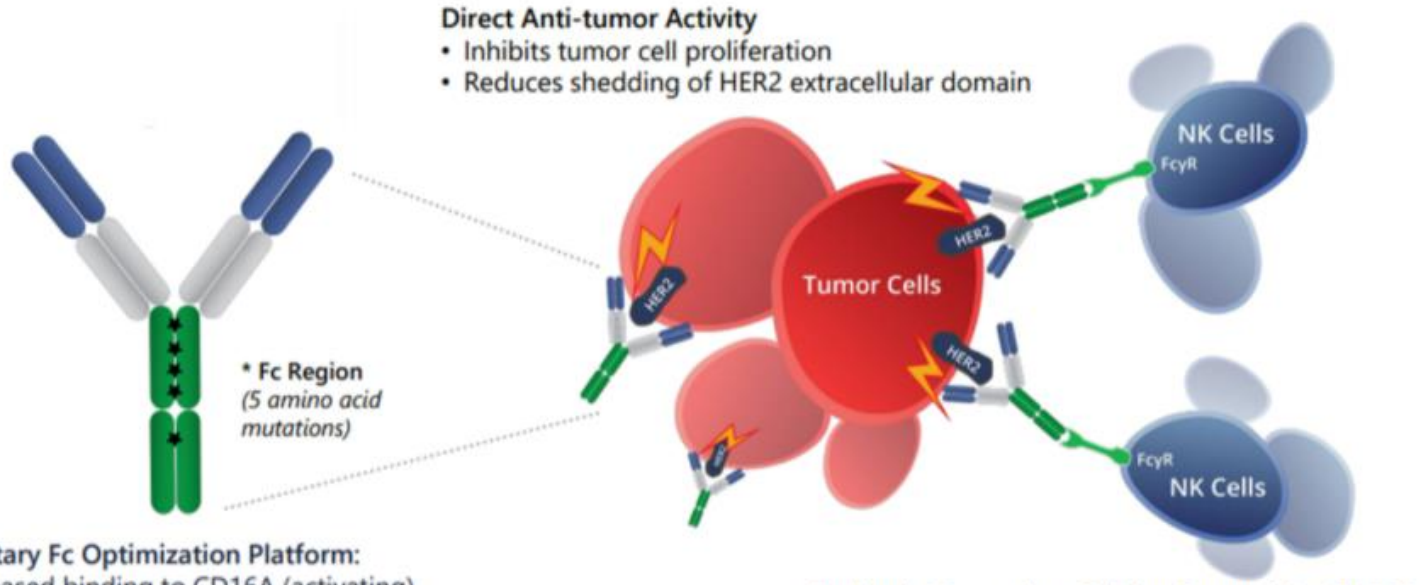


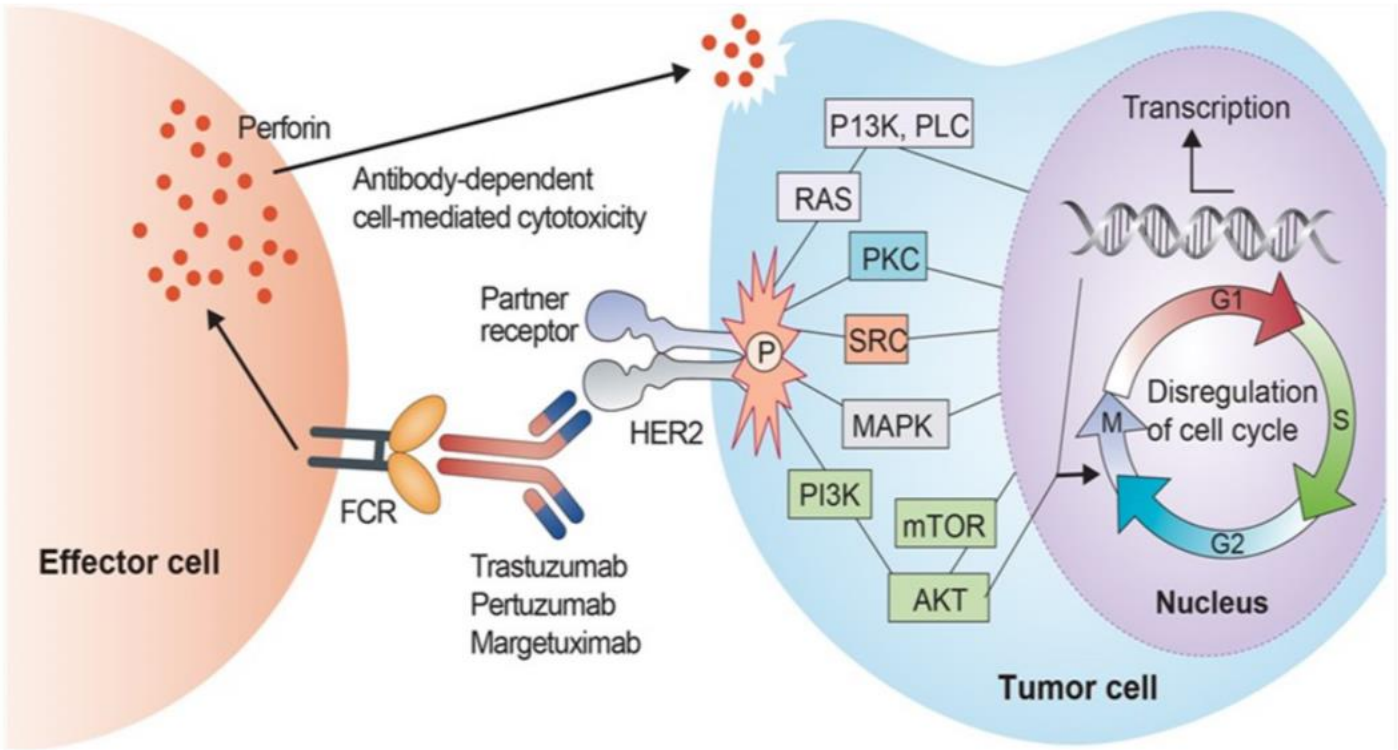
Margetuximab

Margetuximab: Fc optimized chimeric anti-HER2 antibody



Macrogenics Corporate presentation

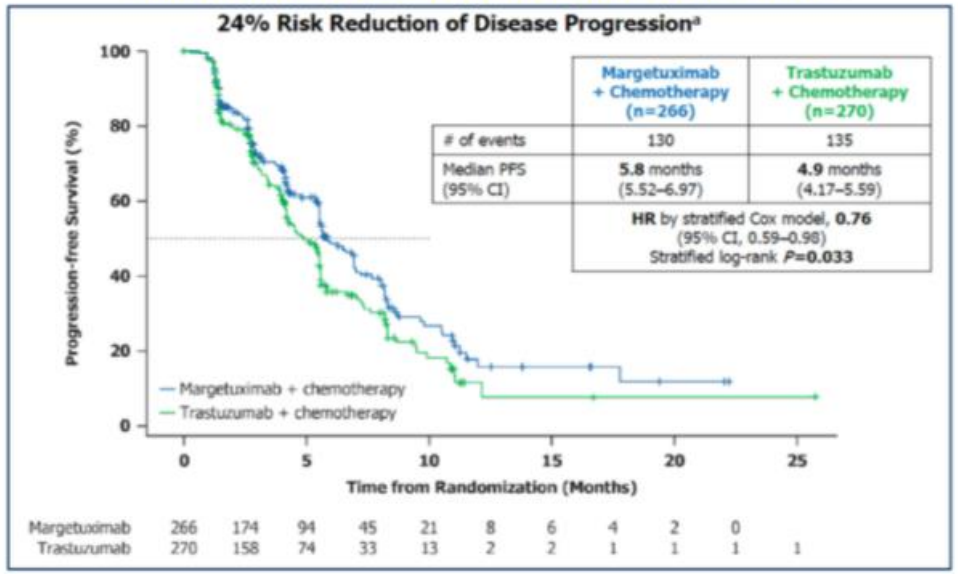
ASCO Meeting Library



Creative Biolabs Inc. https://www.creativebiolabs.net/margetuximab-overview.htm

Margetuximab + chemo: Efficacy in HER2+ MBC

SOPHIA - Progression-free survival (BICR*)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)
HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank *P*=**0.033**		

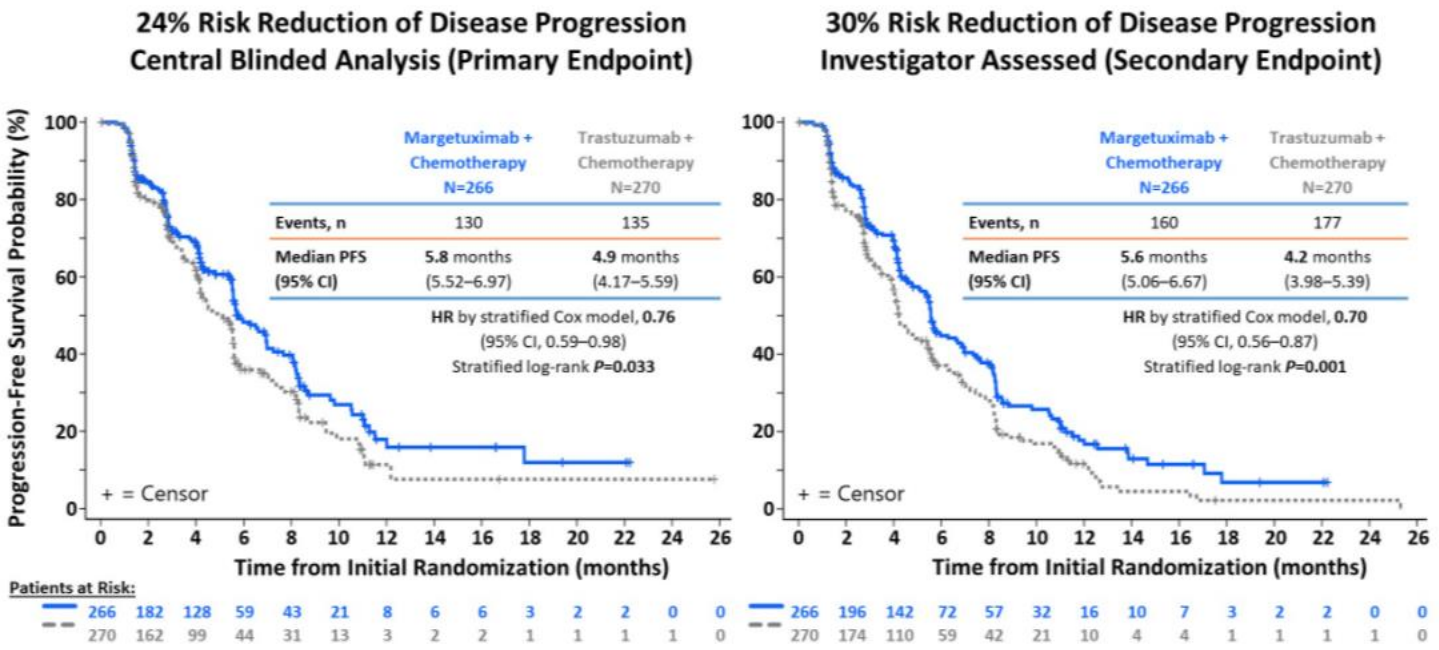
* Blinded independent central review

On December 16, 2020, the FDA approved Margetuximab in combination with chemotherapy, for the treatment of patients with metastatic HER2-positive breast cancer who have received ≥2 prior anti-HER2 regimens, at least one of which was for metastatic disease

HS Rugo et al SABCS 2019

ASCO Meeting Library

Margetuximab Prolongs PFS in ITT Population



Nuevas terapias antiHer2 en cáncer de mama

Emerging treatment options for metastatic HER2 positive breast cancer under investigation

1. Novel anti-HER2 antibodies
2. Bispecific antibodies
3. T-cell dependend bispecific antibodies
4. Antibody-drug conjugates (ADC)
5. Tyrosine kinase inhibitors (TKI)
6. CDK 4/6 inhibitors
7. Immune checkpoint inhibitors

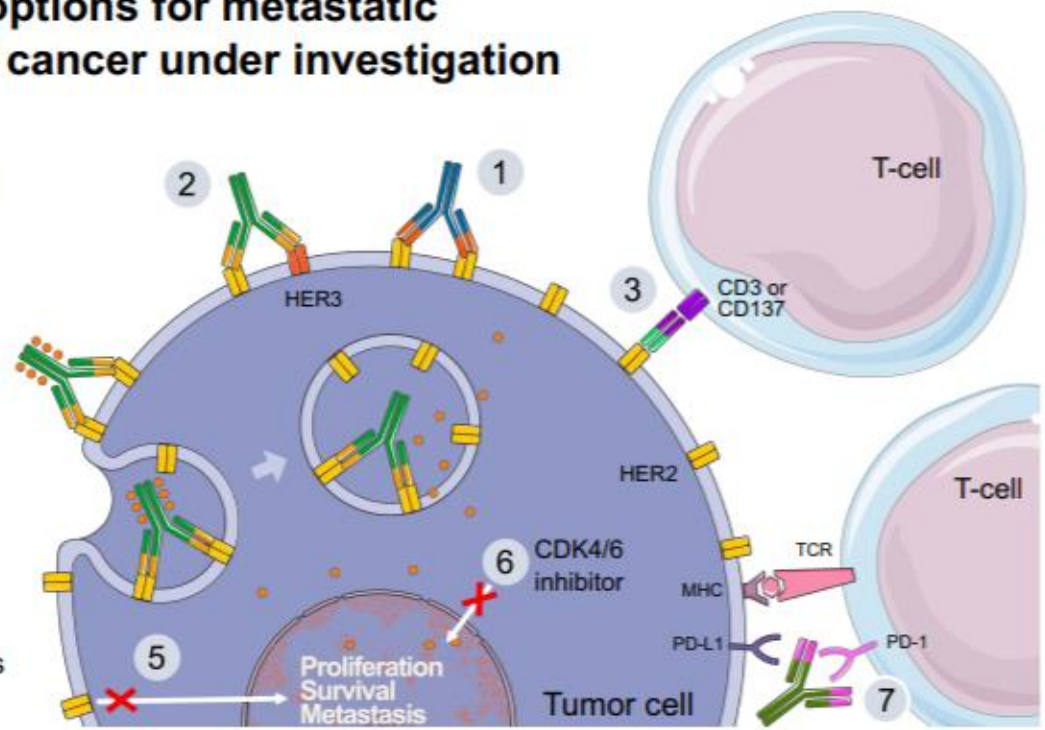


Figure 1 New treatment strategies for HER2-positive MBC discussed in this review. (1) Novel anti-HER2 antibodies bind to the extracellular domain of HER2 and activate the antibody-dependent cell-mediated cytotoxicity (ADCC) more efficiently than trastuzumab; (2) Bispecific antibodies bind to two different epitopes either on HER2 or on HER2 and HER3; (3) T-cell dependent bispecific (TDB) antibodies bind to HER2 on one hand and to an epitope on T cells on the other hand thereby activating the adaptive immune system; (4) Antibody-drug conjugates (ADCs) use the specificity of HER2-directed antibodies to deliver a highly potent chemotherapy directly into the tumor cell; (5) Tyrosine kinase inhibitors (TKIs) are orally available small molecules that block the intracellular domain of HER2 and other receptors of the HER family; (6) CDK4/6 inhibitors block the common final path of several growth factor signaling pathways, including the one of HER2; (7) Currently available immune checkpoint inhibitors target the programmed cell death protein 1 (PD-1) or its ligand PD-L1 and release the "break" in the adaptive immune system.

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Table 1 Overview of New Treatment Options for HER2-Positive MBC, Their Phase of Development and Currently Running Trials. Phase 2 and 3 Trials with Published Results are Highlighted in Bold

	Substance Group	Phase of Development (ClinicalTrials.gov Identifier)	Study Arms and Purpose
Margetuximab	Monoclonal antibody (mAb)	**Phase 3 SOPHIA[14] NCT02492711**	**Margetuximab + chemotherapy vs Trastuzumab (T) + chemotherapy**
ZW25	Bispecific antibody	Phase 1 NCT02892123 Phase 1 b/2 NCT04276493 Phase 2 NCT04224272	Part 1: dose escalation Part 2/3: ZW25 alone and in combination with chemotherapy Cohort 1: ZW25 + docetaxel Part 1: safety and tolerability Part 2: efficacy of ZW25 + palbociclib + fulvestrant
Zenocutuzumab (MCLA-128)	Bispecific antibody	**Phase 2[15] NCT03321981**	**Cohort 1: Zenocutuzumab + T ± vinorelbine**
GBR1302 (ISB 1302)	T-cell dependent (CD3) bispecific antibody	Phase 1/2 NCT03983395	Dose escalation
BTRC4017A	T-cell dependent (CD3) bispecific antibody	Phase 1 NCT03448042	Dose escalation
PRS-343	T-cell dependent (CD137) bispecific antibody	Phase 1 NCT03330561 Phase 1 NCT03650348	Dose escalation Dose escalation in combination with atezolizumab
Trastuzumab deruxtecan (DS-8201a)	Antibody-drug conjugate	Phase 1 NCT02564900 **Phase 2 DESTINY-Breast01[16] NCT03248492**	Dose escalation Part 1: recommended part 2-dose **Part 2: safety and efficacy as single agent in T-DM1 resistant/refractory patients**

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Trastuzumab deruxtecan (DS-8201a)	Antibody-drug conjugate	Phase I NCT02564900 **Phase 2 DESTINY-Breast01 [16] NCT03248492** Phase 3 DESTINY-Breast02 NCT03523585 Phase 3 DESTINY-Breast03 NCT03529110 Phase 3 DESTINY Breast04 NCT03734029	Dose escalation Part 1: recommended part 2-dose **Part 2: safety and efficacy as single agent in T-DM1 resistant/refractory patients** T-deruxtecan vs T + Capecitabine (C) vs Lapatinib (L) + C T-deruxtecan vs T-DM1 T-deruxtecan vs physician's choice treatment
Trastuzumab duocarmazine (SYD985)	Antibody-drug conjugate	Phase I NCT02277717 Phase 3 TULIP NCT03262935	Dose escalation T duocarmazine vs physician's choice treatment
BAT8001	Antibody-drug conjugate	Phase I NCT04189211 Phase 3 NCT04185649	Dose escalation and safety BAT8001 vs L + C
RC48-ADC (hertuzumab-vc-MMAE)	Antibody-drug conjugate	Phase I NCT02881138 Phase Ib NCT03052634 Phase 2 NCT03500380	Dose escalation and safety Recommended phase 2 dose RC48-ADC vs L + C
ARX788	Antibody-drug conjugate	Phase I CTR20171162	Dose escalation, safety and efficacy
ALT-P7	Antibody-drug conjugate	Phase I NCT03281824	Dose escalation, safety and efficacy
Neratinib	Irreversible pan-HER tyrosine kinase inhibitor	**Phase 2 [17] NCT00300781** **Phase 2 [18] NCT00777101**	**Efficacy of neratinib in T-pretreated and T-non pretreated patients** **Neratinib vs L + C**

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	Substance Group	Phase of Development (ClinicalTrials.gov Identifier)	Study Arms and Purpose
		Phase 2 NEfERT-T[19] NCT00915018	**Neratinib + paclitaxel vs T + Paclitaxel**
		Phase 1b/2 NSABP FB-10[20] NCT02236000	**Dose escalation and efficacy of Neratinib + T-DM1**
		Phase 2 TBCRC 022[21] NCT01494662	**Cohort 3a/3b: efficacy of neratinib + C in CNS-MBC**
		Phase 3 NALA[22] NCT01808573	**Neratinib + C vs L + C**
Pyrotinib	Irreversible pan-HER tyrosine kinase inhibitor	Phase 1 NCT01937689 **Phase 2[23] NCT02422199** **Phase 3 PHOEBE[24] NCT03080805**	Dose escalation, safety and efficacy **Pyrotinib + C vs L + C** **Pyrotinib + C vs L + C**
Tucatinib	Selective HER2 tyrosine kinase inhibitor	Phase 1b NCT02025192 **Phase 2 HER2CLIMB[25] NCT02614794**	Efficacy and Safety of tucatinib + T ± capecitabine **Tucatinib + T + C vs placebo + T + C**
Abemaciclib	CDK4/6 inhibitor	**Phase 2 MonarcHER[26] NCT02675231**	**Abemaciclib + T + fulvestrant vs Abemaciclib + T vs T + physician's choice treatment**

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Palbociclib	CDK4/6 inhibitor	**Phase 2 PATRICIA[27] NCT02448420**	**Part 1: Palbociclib + T ± letrozole Part 2: Palbociclib + T + endocrine therapy vs T + physician's choice treatment (T-DM1 or chemotherapy)**
Pembrolizumab	Checkpoint inhibitor (CPI), anti-PD-1 mAb	**Phase 1b-2 PANACEA[28] NCT02129556**	**Safety and efficacy of Pembrolizumab + T in T-resistant MBC**
Atezolizumab	CPI, anti-PD-L1 mAb	**Phase 2 KATE2[29,30] NCT02924883** Phase 3 NCT03199885	**T-DM1 + atezolizumab vs T-DM1 + placebo** T + pertuzumab (P)+ paclitaxel + atezolizumab vs T+P+paclitaxel +placebo
Avelumab	CPI, anti-PD-L1 mAb	Phase 2 AVIATOR NCT03414658	T + vinorelbine + avelumab ± utomilumab (4IBB/CD137 agonist)

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¡Muchas gracias!