Nuove strategie nella malattia avanzata HER2 positiva

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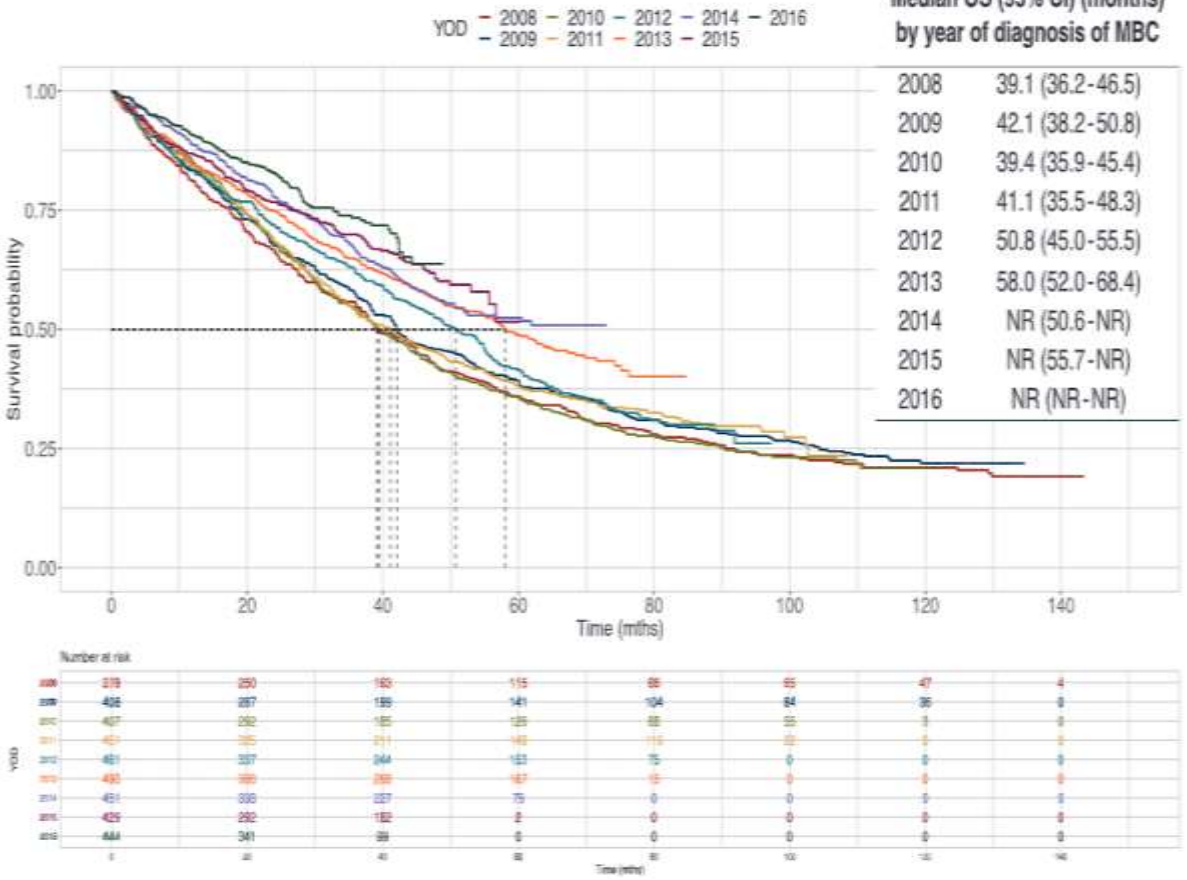
Real-world OS of HER2+ MBC over time



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

Definizione tumore mammario HER2 positivo

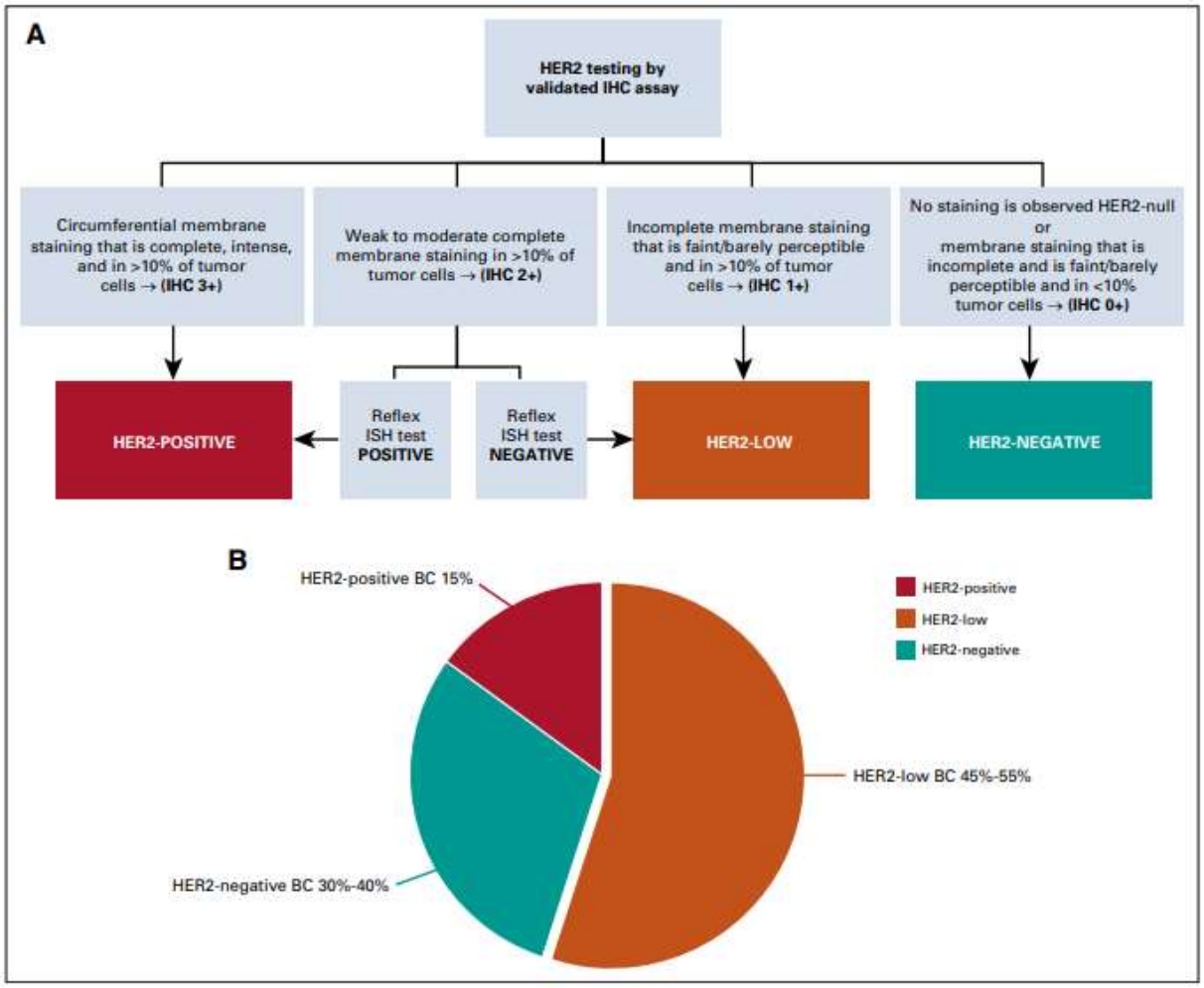
- In Italia si stimano circa 55.700 nuovi casi di tumore mammario ogni anno. La neoplasia mammaria rappresenta la neoplasia più frequente in assoluto per incidenza nella popolazione femminile e rappresenta il 30% di tutte le nuove diagnosi di tumore. In media, in assenza di condizioni particolari (come la mutazione genetica), il rischio di ciascuna donna di ammalarsi è del 10-12%

- La sigla HER2 si riferisce al recettore 2 per il fattore di crescita epiteliale (Human Epidermal Growth Factor Receptor 2). In alcuni tipi di tumori, in particolare nel tumore alla mammella o nel tumore gastroesofageo, le cellule tumorali presentano più di due copie del gene che codifica per questa proteina, con la conseguente iperproduzione della stessa

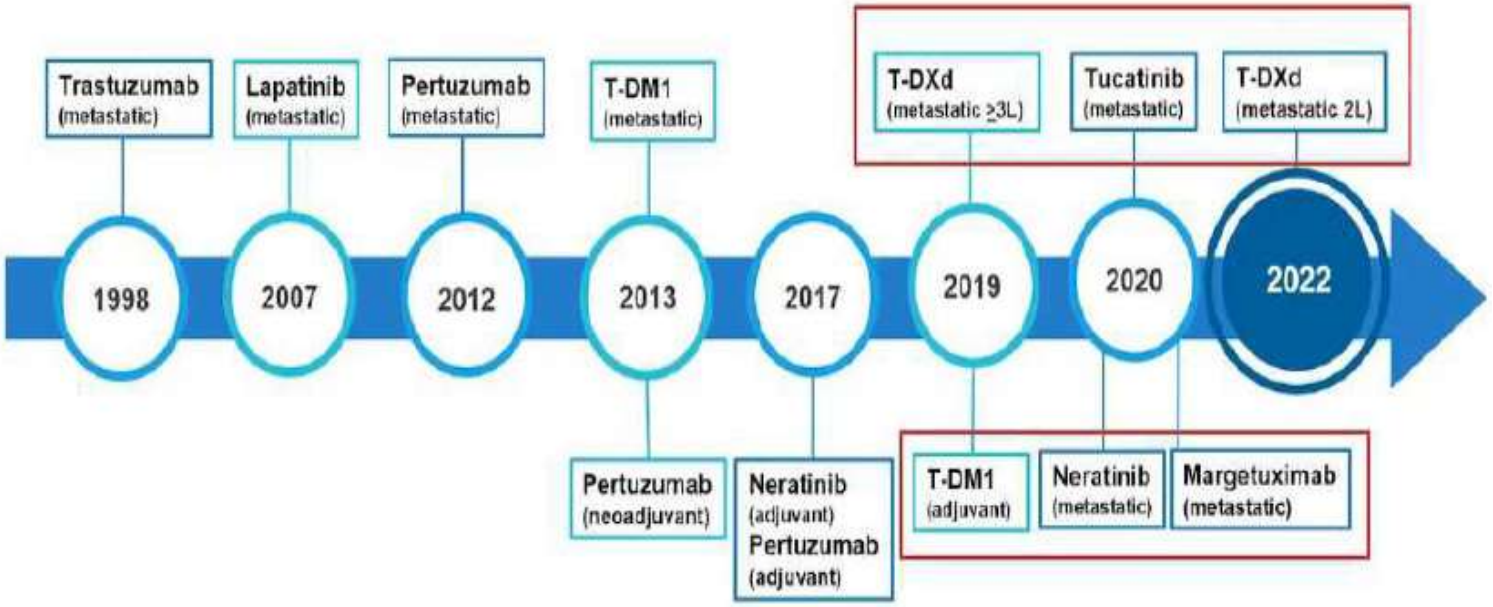
- I tumori caratterizzati dall'iperespressione di HER2 sono noti come HER2-positivi. Il test per HER2 eseguito su un campione di tessuto tumorale identifica i tumori come HER2-positivi o negativi. Il 15-20 % dei tumori della mammella sono HER2 +

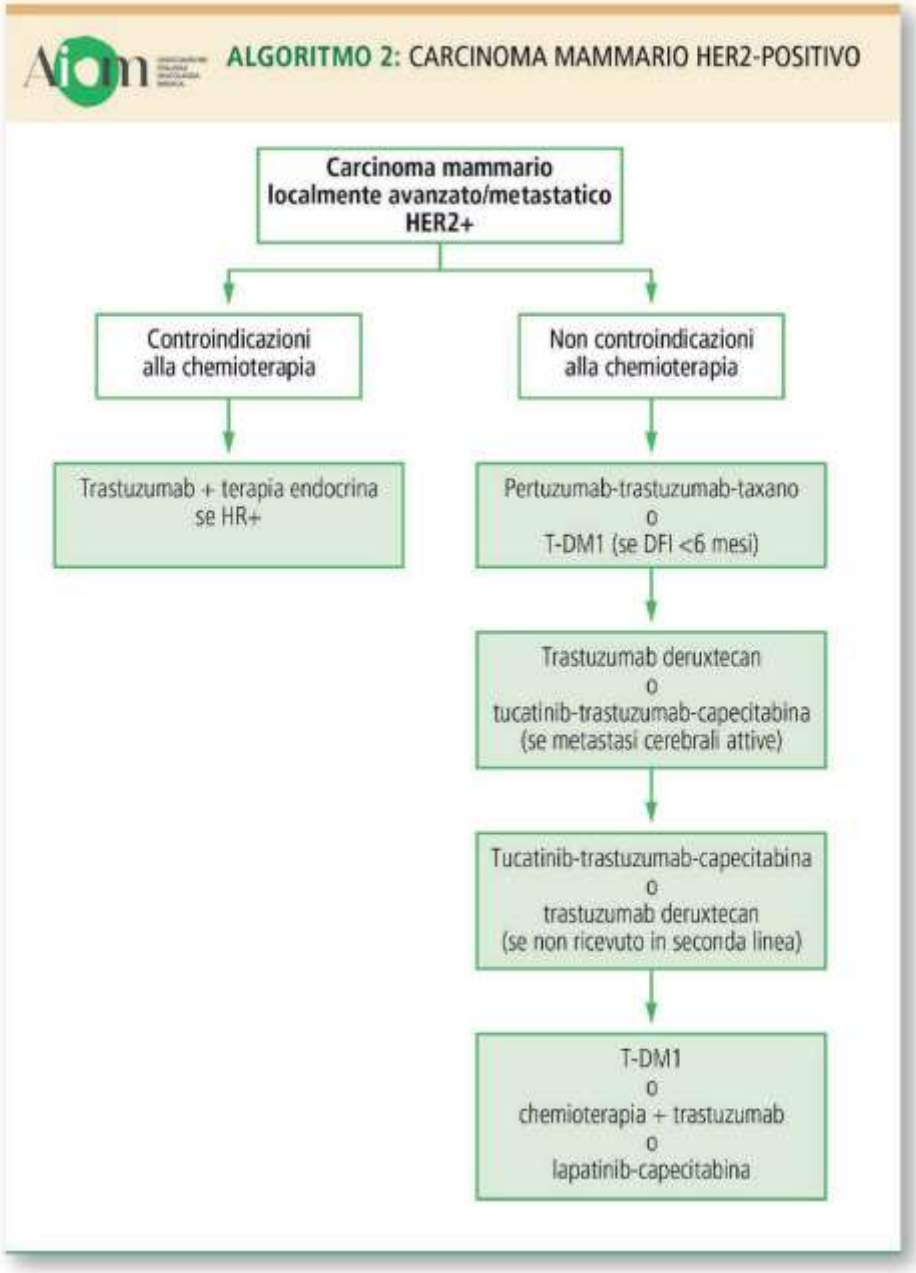
- Nelle cellule normali, il gene HER2 codifica per una proteina responsabile della promozione della crescita cellulare. L'amplificazione o l'iperespressione del gene HER2 si traduce in un’amplificazione del segnale di crescita cellulare.

Espressione HER2 nel tumore della mammella



Terapie approvate dall' FDA per il tumore della mammella HER2 + (2022)

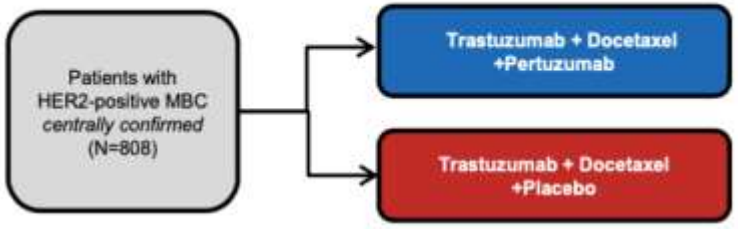


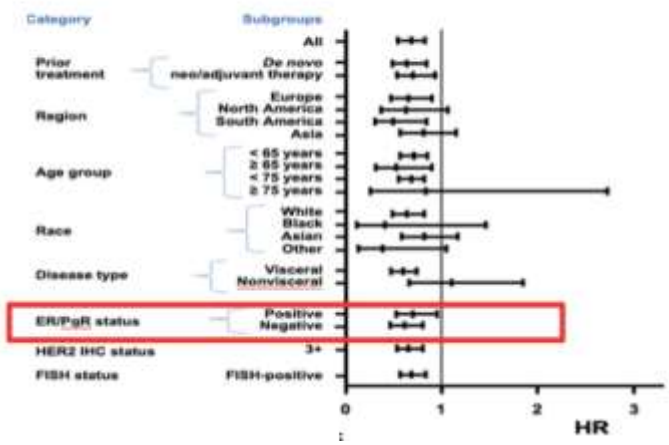


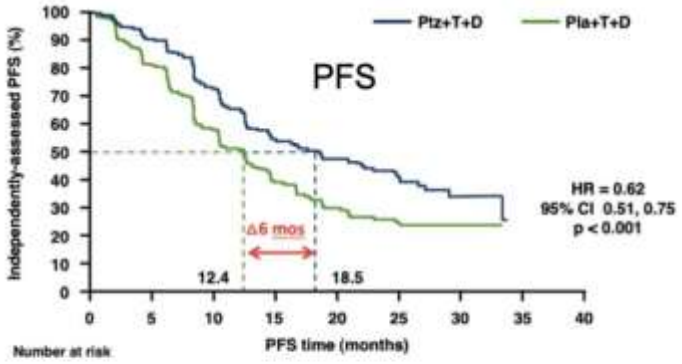
Linee Guida AIOM tumore della mammella 2023

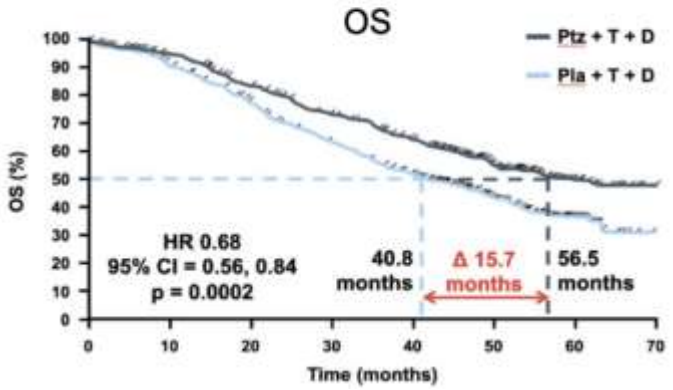
Trattamento di prima linea per la malattia avanzata HER2 +

Cleopatra trial
Docetaxel + Trastuzumab + Pertuzumab: vantaggio in PFS and OS





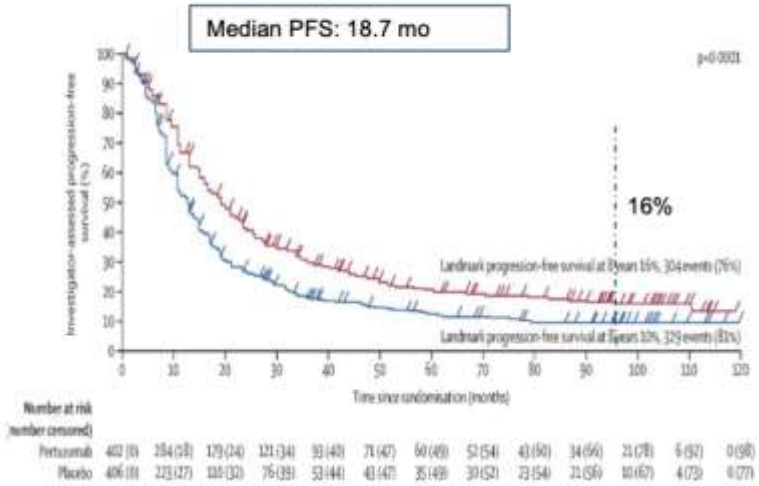


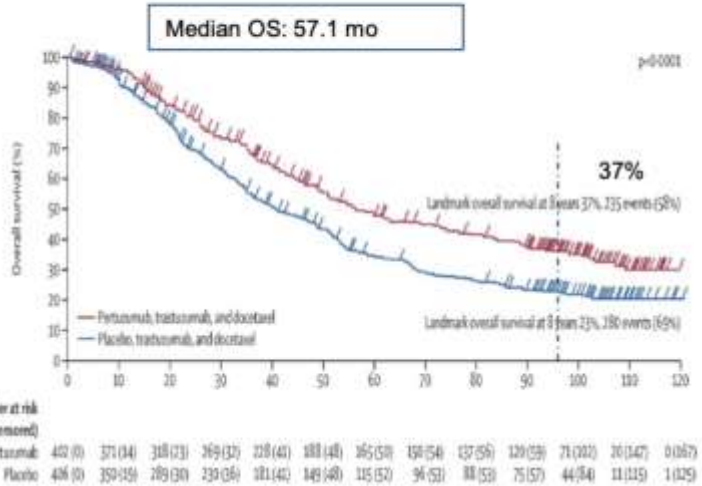


Baselga J et al, NEJM 2012; Swain S et al, NEJM 2015

Cleopatra trial: risultati al termine dello studio

(median follow-up ~100 months)





Swain S et al, Lancet Oncol 2020

Cleopatra: tossicità

Table 6 Ten most common grade ≥3 adverse events overall

n (%)	<65 years		≥65 years	
	Placebo + trastuzumab + docetaxel (*n* = 332)	Pertuzumab + trastuzumab + docetaxel (*n* = 346)	Placebo + trastuzumab + docetaxel (*n* = 65)	Pertuzumab + trastuzumab + docetaxel (*n* = 61)
Total number of patients with at least one grade ≥ 3 adverse event	241 (72.6)	255 (73.7)	48 (73.8)	47 (77.0)
Blood and lymphatic system disorders	184 (55.4)	210 (60.7)	31 (47.7)	30 (49.2)
Neutropenia	156 (47.0)	174 (50.3)	26 (40.0)	25 (41.0)
Leukopenia	51 (15.4)	44 (12.7)	7 (10.8)	6 (9.8)
Febrile neutropenia	26 (7.8)	51 (14.7)	4 (6.2)	5 (8.2)
Diarrhoea	16 (4.8)	23 (6.6)	4 (6.2)	9 (14.8)
Anaemia	9 (2.7)	10 (2.9)	5 (7.7)	0 (0.0)
Fatigue	9 (2.7)	7 (2.0)	4 (6.2)	2 (3.3)
Peripheral neuropathy	6 (1.8)	6 (1.7)	1 (1.5)	5 (8.2)
LVSD	8 (2.4)	4 (1.2)	3 (4.6)	1 (1.6)
Asthenia	4 (1.2)	10 (2.9)	2 (3.1)	0 (0.0)
Granulocytopenia	9 (2.7)	4 (1.2)	0 (0.0)	2 (3.3)

LVSD left ventricular systolic dysfunction

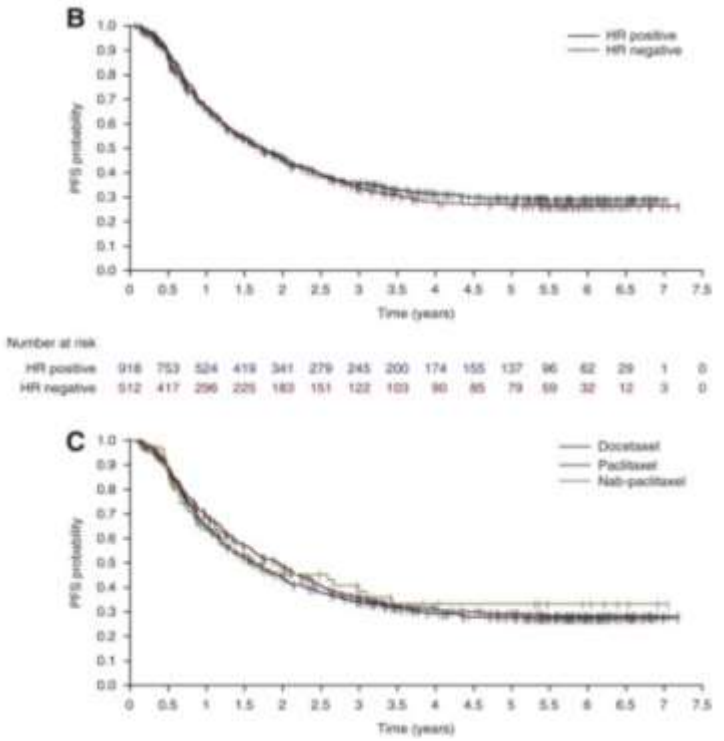
Miles D, Breast Cancer Res Treat , 2013

Peruse trial: studio Trastuzumab + Pertuzumab + Taxano Docetaxel vs Paclitaxel vs Nab-paclitaxel

Median PFS was 20.7m and similar regardless of taxane backbone or HR status

Median OS was 65 m and was similar regardless of taxane; it was longer for HR+ cases, lending support for the use of maintenance ET

N=1436; Median f/u approx. 6 yrs



Miles D et al, Ann of Oncol 2021

Take home message

- Il trattamento di prima linea nel tumore della mammella avanzato HER2 + è rappresentato da taxani + pertuzumab + trastuzumab per 6-8 cicli → terapia di mantenimento con trastuzumab e pertuzumab

- La aggiunta del pertuzumab al trastuzumab e taxano determina un aumento statisticamente e clinicamente significativo della sopravvivenza libera da progressione e della sopravvivenza globale

- Il trattamento con terapia antiHER2 non impatta in modo importante sulla tossicità che risulta essere attribuibile maggiormente alla chemioterapia

- Non vengono evidenziate tossicità inattese negli studi clinici.

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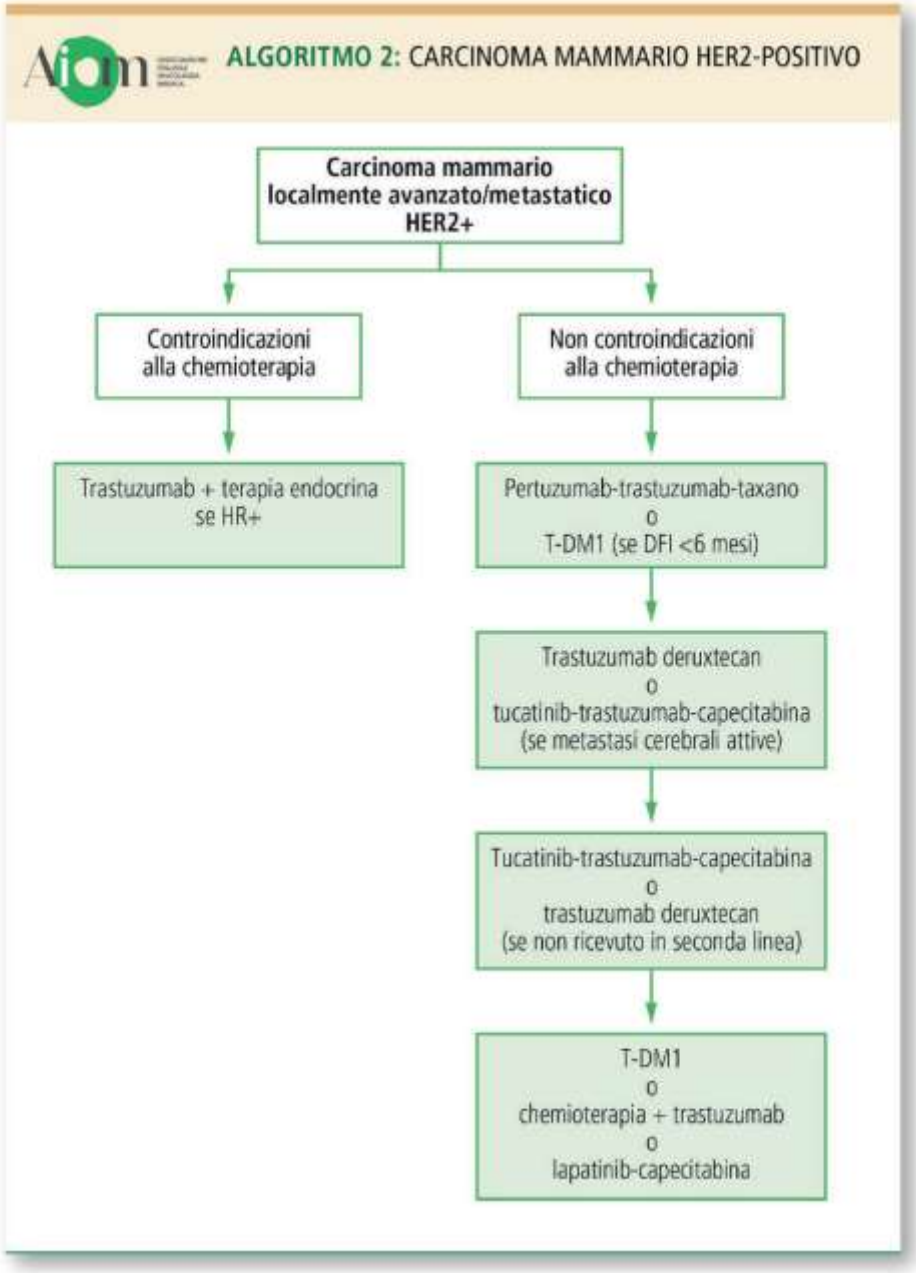
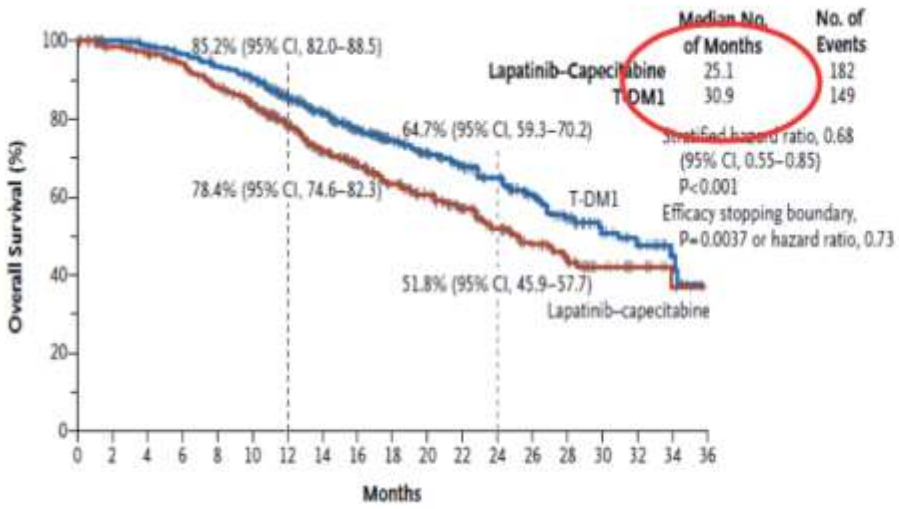
Trattamento di seconda linea per la malattia avanzata HER2 +



Linee Guida AIOM tumore della mammella 2023

EMILIA trial: TDM1 vs Lapatinib + Capecitabine
Improvement of PFS and OS with TDM1



	Cap + Lap (n=488)	T-DM1 (n=490)
All-grade AE, n (%)	477 (97.7)	470 (95.9)
Grade ≥3 AE, n (%)	278 (57.0)	200 (40.8)
AEs leading to treatment discontinuation (for any study drug), n (%)	52 (10.7)	29 (5.9)
AEs leading to death on treatment, n (%)[a]	5 (1.0)	1 (0.2)
Cardiac dysfunction AEs,[a] n (%)		
All grades	15 (3.1)	9 (1.8)
Grade 3	2 (0.4)	1 (0.2)
LVEF <50% and ≥15-point decrease from baseline, %[b]	7 (1.6)	8 (1.7)

Verma S et al, NEJM 2012

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Lapatinib plus Capecitabine (N=488)		T-DM1 (N=490)	
	Events of Any Grade	Events of Grade 3 or Above	Events of Any Grade	Events of Grade 3 or Above
	number of patients (percent)			
Any event	477 (97.7)	278 (57.0)	470 (95.9)	200 (40.8)
Specific events†				
Diarrhea	389 (79.7)	101 (20.7)	114 (23.3)	8 (1.6)
Palmar–plantar erythrodysesthesia	283 (58.0)	80 (16.4)	6 (1.2)	0
Vomiting	143 (29.3)	22 (4.5)	93 (19.0)	4 (0.8)
Neutropenia	42 (8.6)	21 (4.3)	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	20 (4.1)	42 (8.6)	11 (2.2)
Fatigue	136 (27.9)	17 (3.5)	172 (35.1)	12 (2.4)
Nausea	218 (44.7)	12 (2.5)	192 (39.2)	4 (0.8)
Mucosal inflammation	93 (19.1)	11 (2.3)	33 (6.7)	1 (0.2)
Anemia	39 (8.0)	8 (1.6)	51 (10.4)	13 (2.7)
Elevated ALT	43 (8.8)	7 (1.4)	83 (16.9)	14 (2.9)
Elevated AST	46 (9.4)	4 (0.8)	110 (22.4)	21 (4.3)
Thrombocytopenia	12 (2.5)	1 (0.2)	137 (28.0)	63 (12.9)

* The safety population included all patients who received at least one dose of the study treatment. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Listed are adverse events of grade 3 or above with an incidence of 2% or higher in either group.

Verma S et al, NEJM 2012

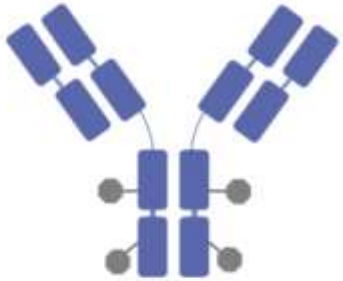
Trastuzumab deruxtecan and trastuzumab emtansine

HER2 Targeting ADCs with similar mAB Backbone

Trastuzumab deruxtecan (T-DXd)[1]

T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



ADC, antibody-drug conjugate; MoA, mechanism of action.
[a]The clinical relevance of these features is under investigation.

1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res.* 2011;17:6437-47.

Cortes, J et al. ESMO 2021

Bystander effect

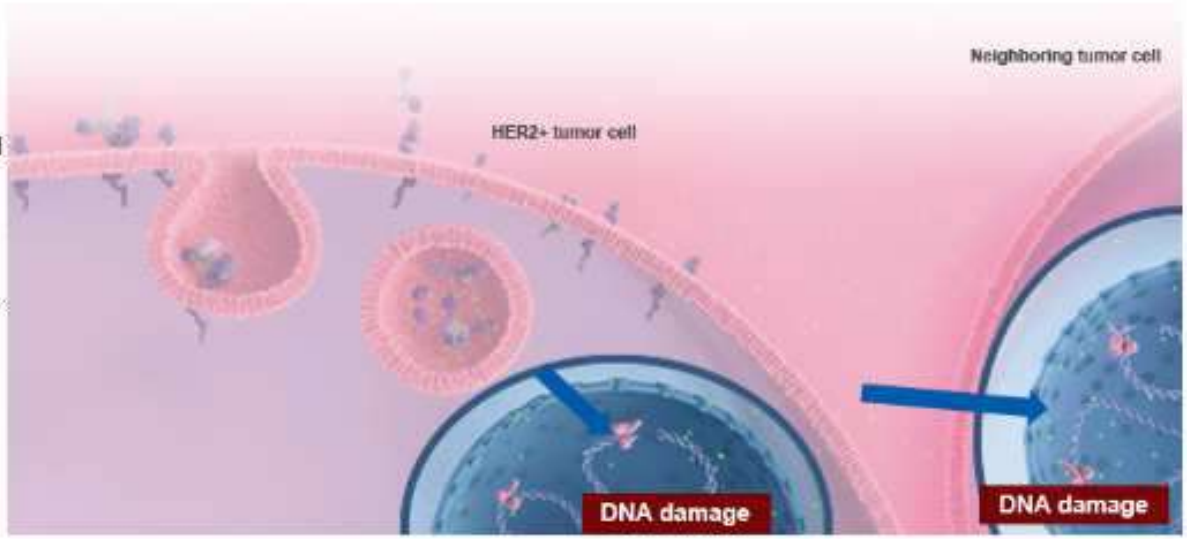
Proposed MOA of T-DXd: Step 4—
Topoisomerase I Inhibitor Payload Enters Tumor Cell Nucleus Leading to DNA Damage

4

Topoisomerase I inhibitor enters tumor cell nucleus

The released payload enters the cell nucleus and causes damage to the tumor cell's DNA[1]

The payload also has high-cell membrane permeability that enables elimination of both target tumor cells and the surrounding tumor cells[2]

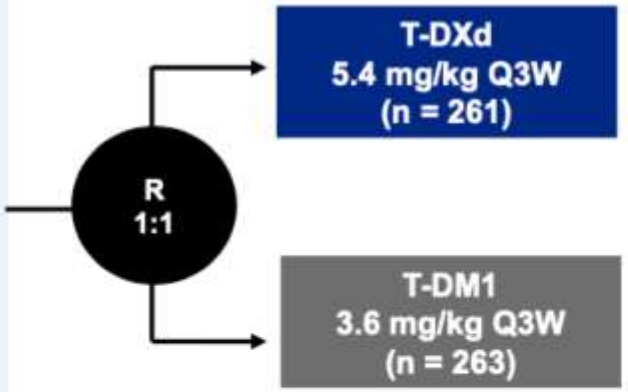


1. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 2. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Destiny-B03: phase 3 randomized trial T-Dxd ≥2nd line open-label multicenter study

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

Prior therapy for MBC:
100% received prior trastuzumab
60% received prior pertuzumab
16% received HER2 TKI
50% received 1 line of therapy for MBC

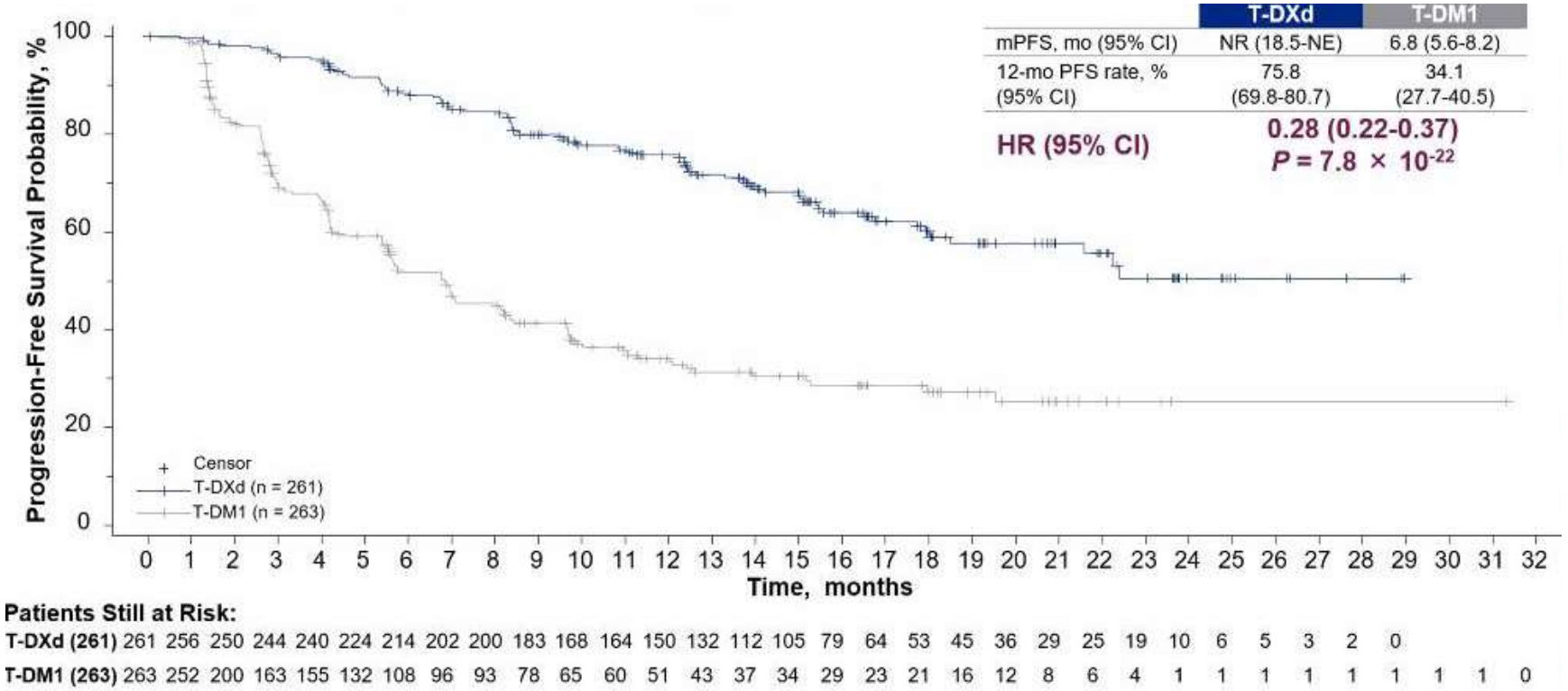
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Cortes, J et al. ESMO 2021

Brain metastasis was not a stratification factor

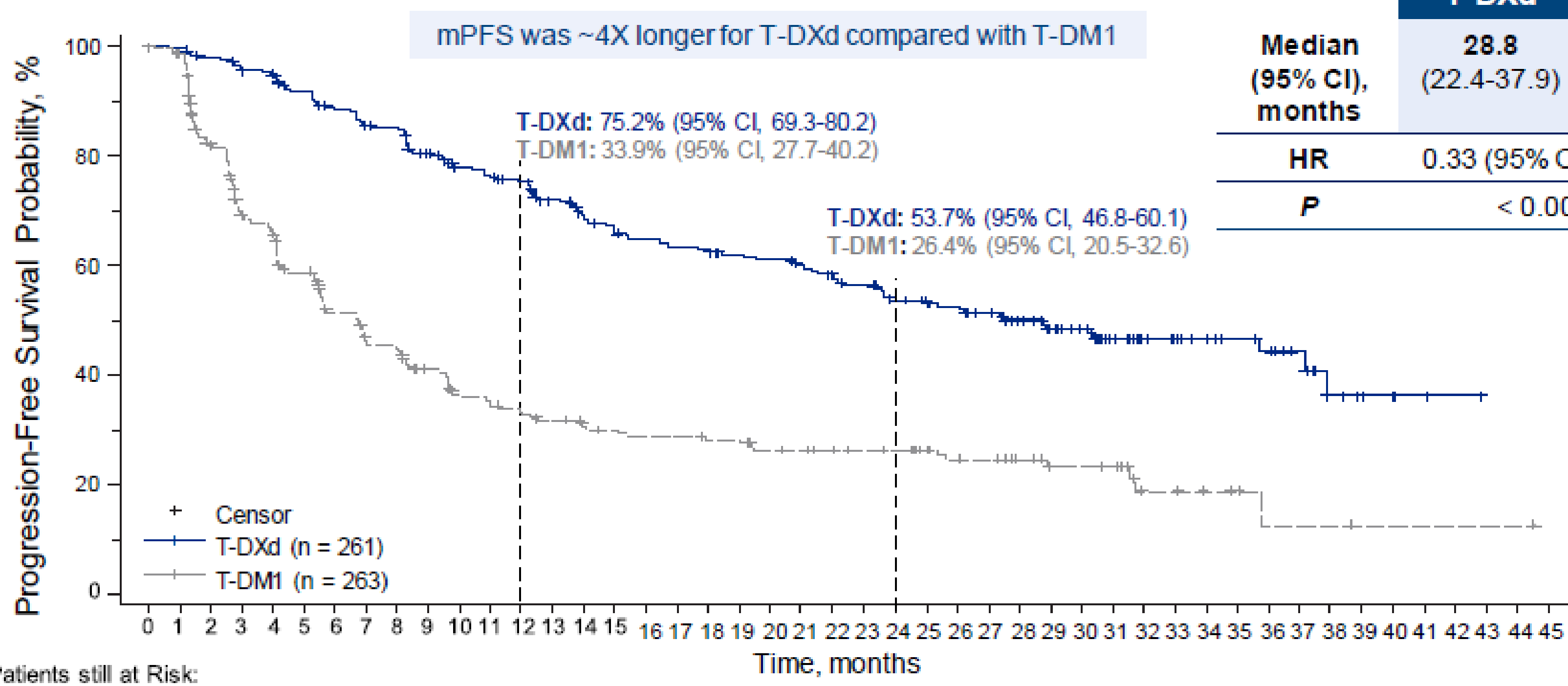
Treated, NON ACTIVE brain metastasis≃50%

Primary Endpoint PFS by BICR



Cortés J et al. *N Engl J Med*. 2022;386:1143-1154

Updated Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Patients still at Risk:

Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39

Month	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
T-DXd	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

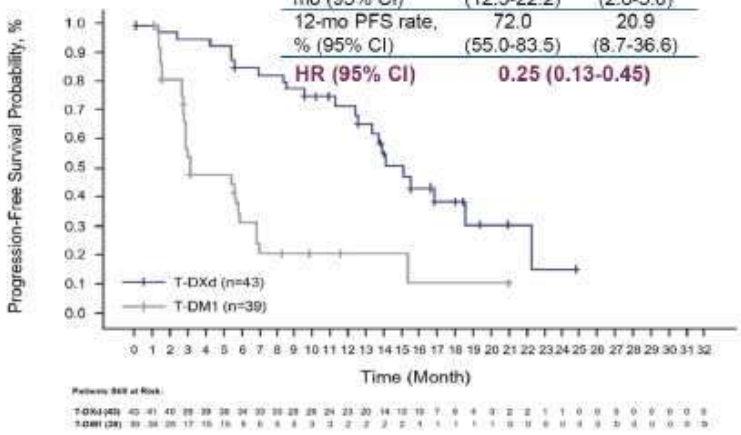
CNS activity of Trastuzumab-Deruxtecan: exploratory analysis of the DB03 trial

Inclusion criteria: stable, treated BM, ≥2 weeks from RT

History of brain mets: n=114, of which → **Brain mets at bsl: n=82**

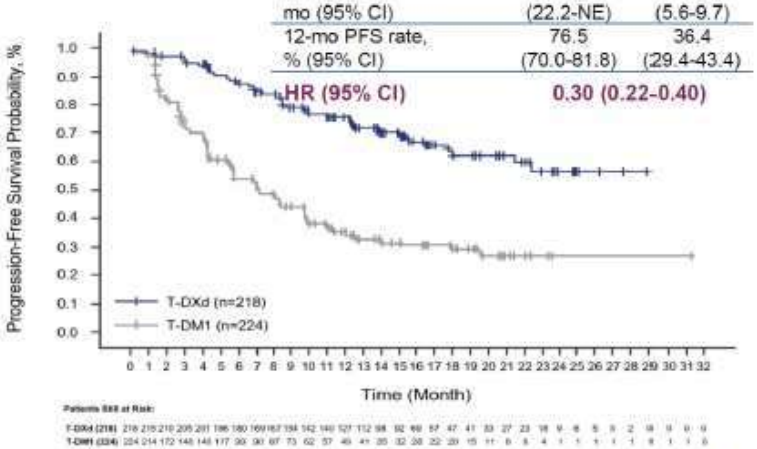
Brain Metastases at Baseline

	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)	



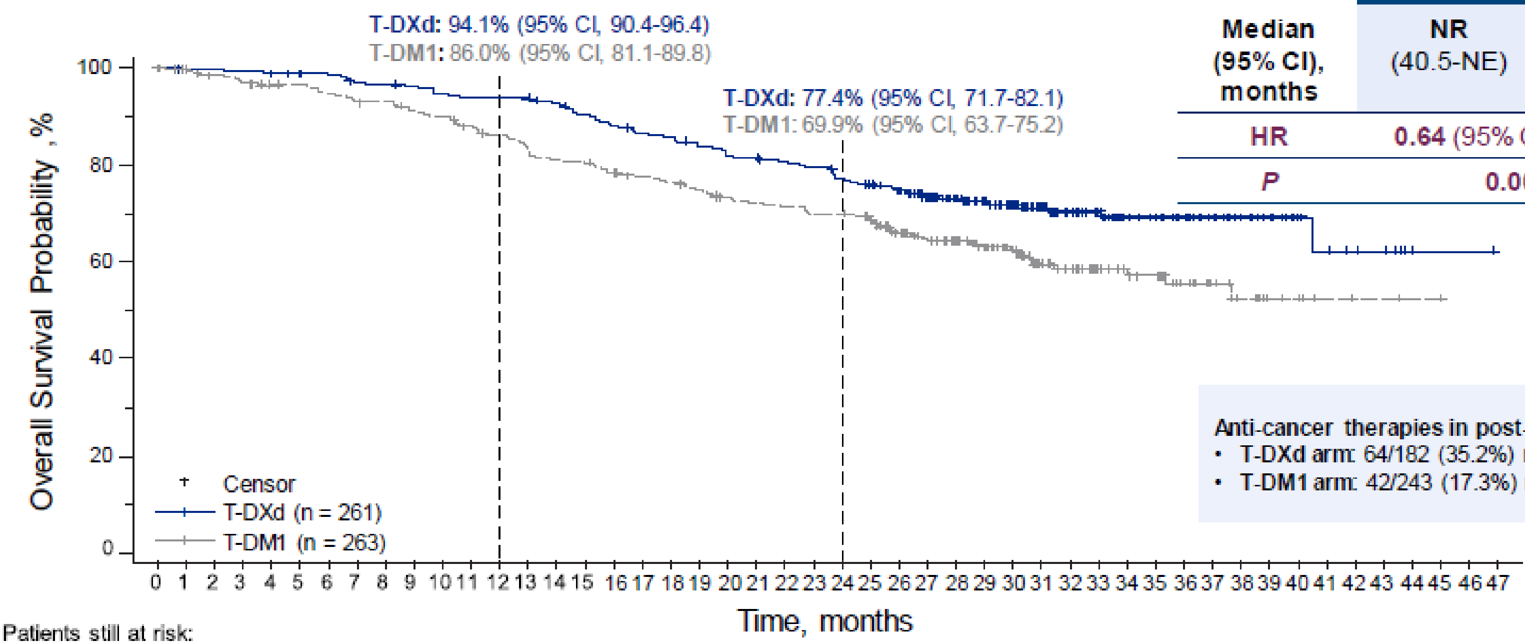
No Brain Metastases at Baseline

	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)	



Hurvitz et al., SABCS 2021 GS3-01

Key Secondary Endpoint: 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

Patients still at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164

	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Eventi avversi di interesse speciale

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)

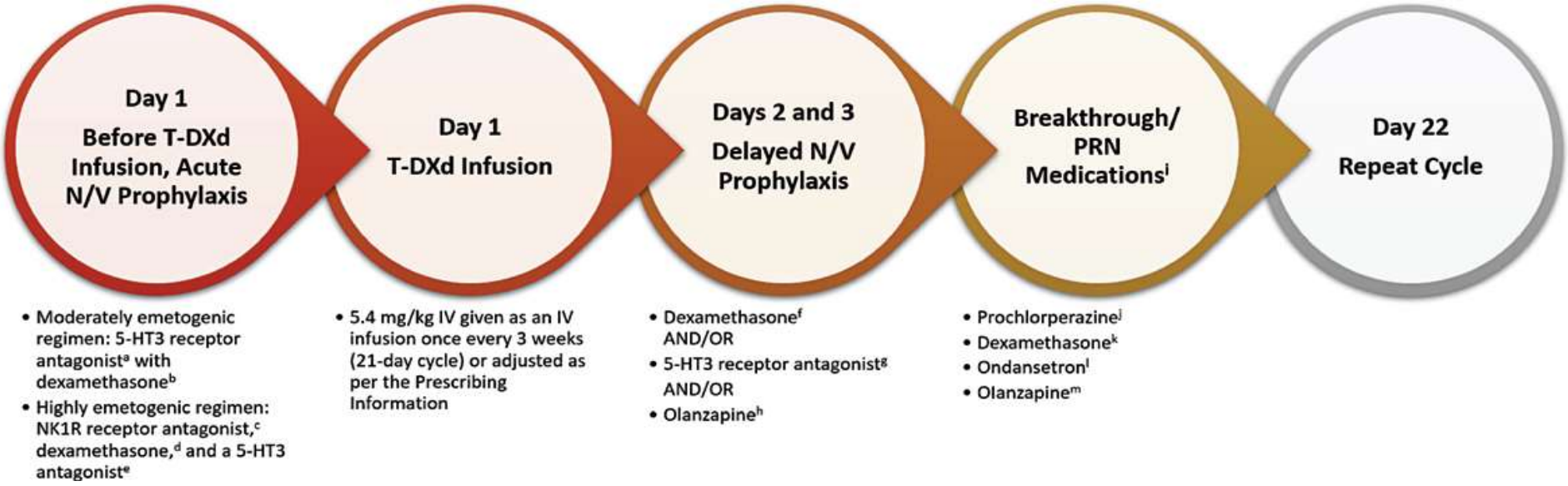
- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF, 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 LVEF adverse events reported were asymptomatic and no cases of cardiac failure occurred

Cortes J et al, ESMO 2021; Cortes J et al, NEJM 2022

Nausea management



Bardia A et al, The Oncologist 2022

Take home message

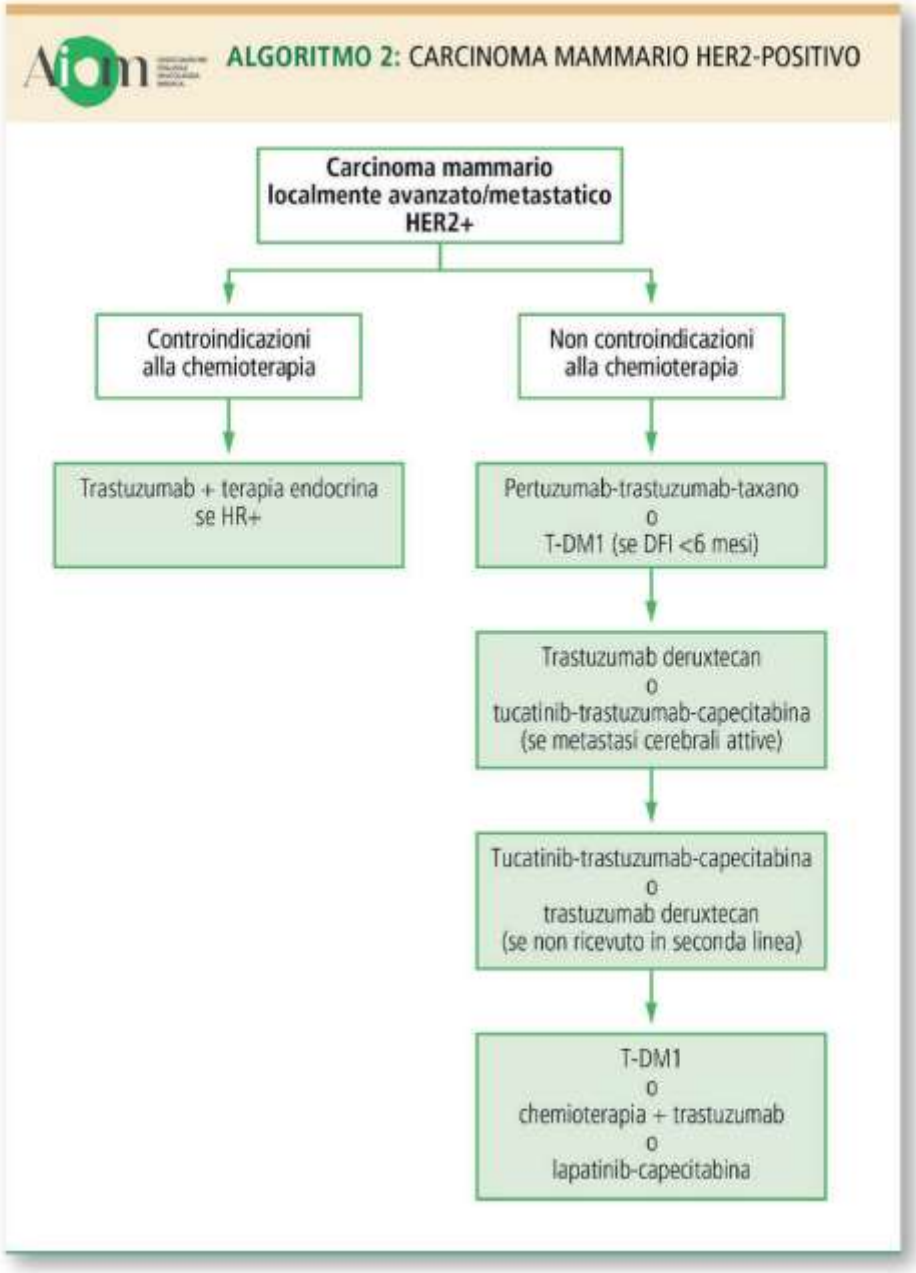
- Il trattamento di seconda linea nel tumore della mammella avanzato HER2 + è rappresentato da trastuzumab deruxtecan: nello studio Destiny 03, nel braccio di trattamento con trastuzumab deruxtecan (Enhertu) si evidenzia un vantaggio statisticamente e clinicamente significativo della sopravvivenza libera da progressione e della sopravvivenza globale rispetto al braccio di controllo con il TDM1 (Kadcyla)

- La terapia con trastuzumab deruxtecan è associata un numero di eventi avversi superiore al TDM-1. Gli eventi avversi più frequenti sono rappresentati da tossicità gastrointestinale.

- Negli studi clinici viene messa in evidenza tossicità polmonare, polmonite insterstiziale.

-

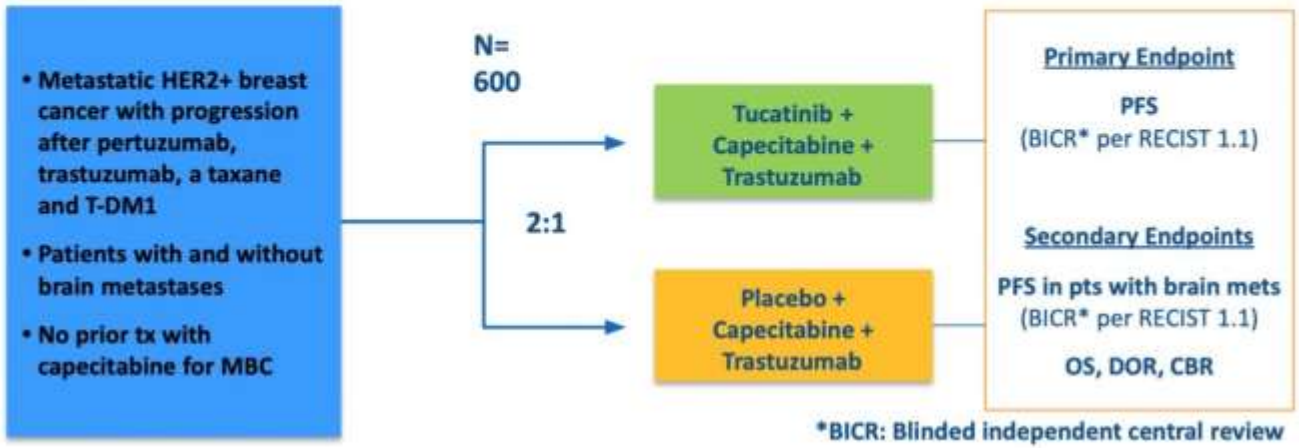
Trattamento di terza linea per la malattia avanzata HER2 +



Linee Guida AIOM tumore della mammella 2023

Tucatinib: new HER2-selective TKI

HER2CLIMB trial: tucatinib, trastuzumab, capecitabine



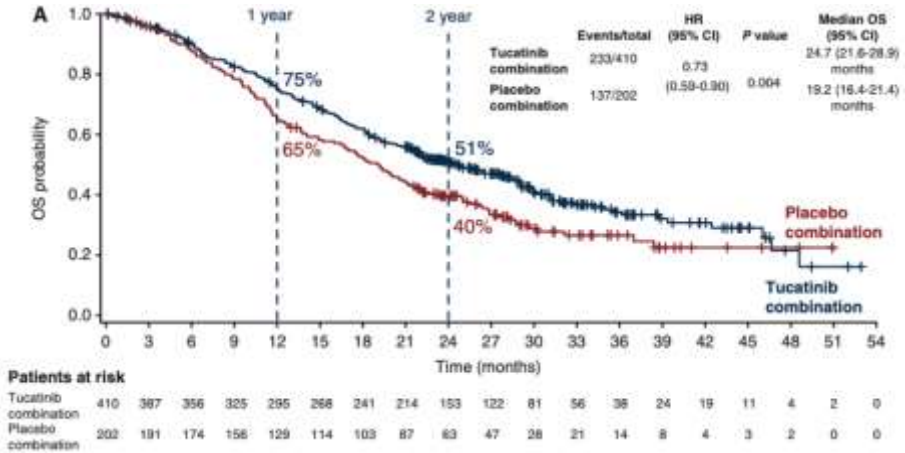
median lines for MBC: 3

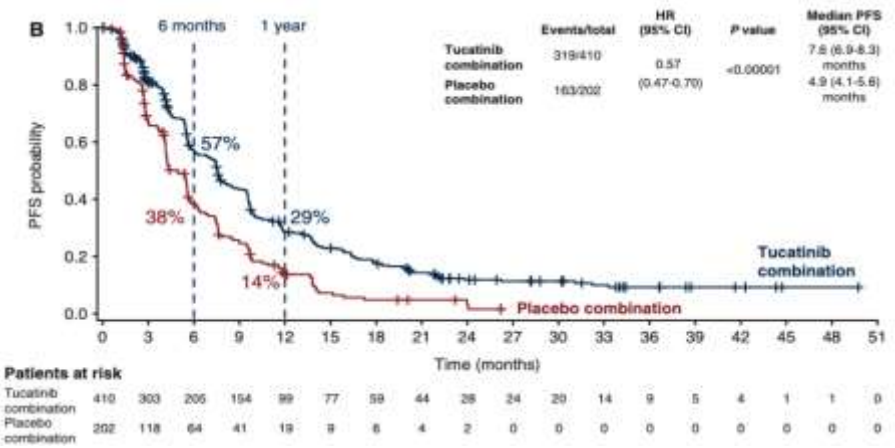
- Key Inclusion/Exclusion Criteria
  - active or treated stable BMs
  - neurologically stable
  - not requiring immediate local therapy (those treated with local therapy after washout could be eligible and included in treated stable group for analysis)
  - no leptomeningeal disease
- Brain MRI at baseline, every 6 weeks for the first 24 weeks, every 9 weeks thereafter.

Curigliano G et al, Ann Onc 2022

HER2CLIMB: Trastuzumab + Capecitabine +/- Tucatinib
Tucatinib improves PFS, OS and ORR

ORR 40.6% vs 22.8% p=0.00008





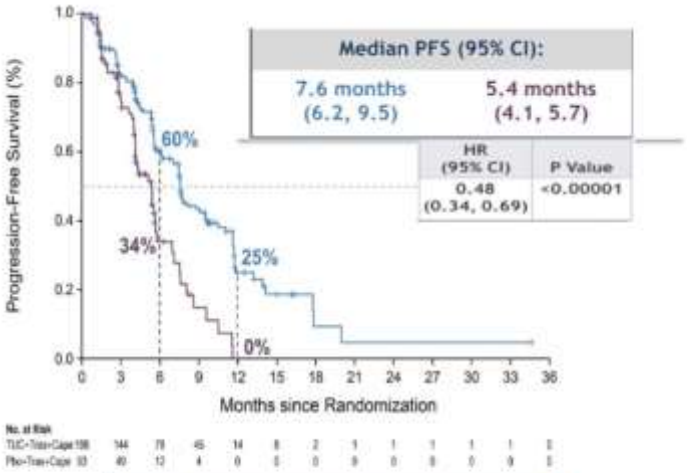
mOS 24.7 m vs 19.2 m HR 0.73 p=0.004
2y-OS rate 51% vs 40%

mPFS 7.6 m vs 4.9 m HR 0.57 p<0.00001
1y-PFS rate 29% vs 14%

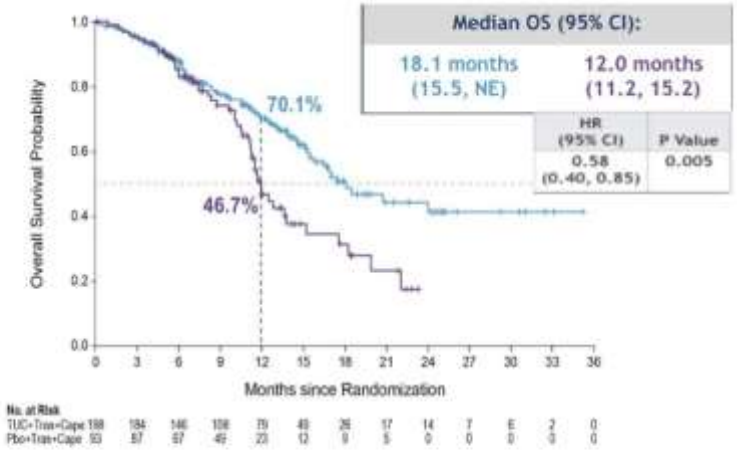
Approvals: FDA 05/2020, EMA 12/2020, AIFA CNN 05/2021 rimborsabilità GU 11/2022

Murthy R et al, NEJM 2020; Curigliano G et al, Ann Oncol 2022

HER2CLIMB: pazienti con metastasi cerebrali



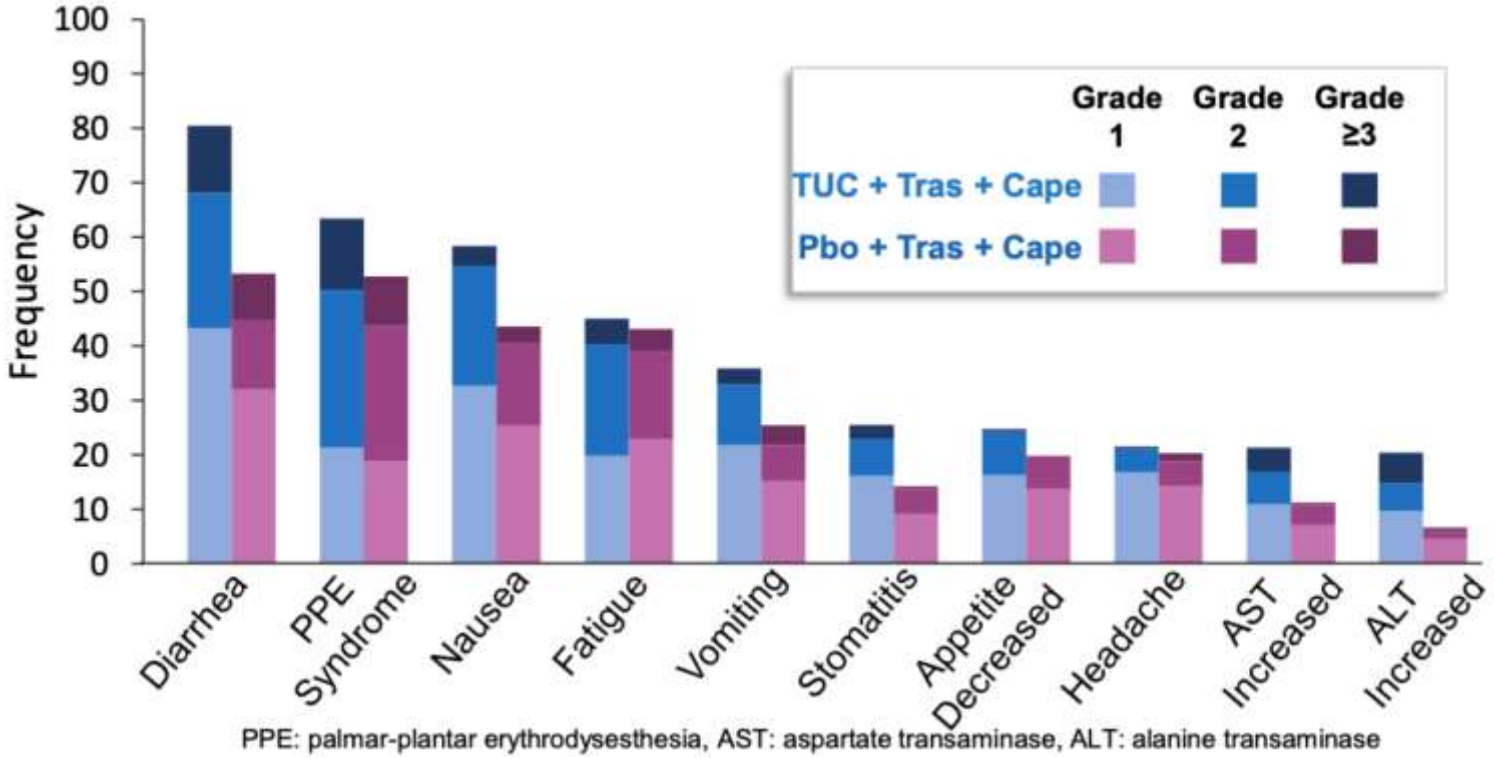
Risk of progression in patients with BM was reduced by 52%



Risk of death in patients with BM was reduced by 42%

Murthy R et al, NEJM 2020; Lin N et al, JCO 2020

HER2CLIMB: eventi avversi ≥20% tucatinib-capecitabine-trastuzumab



Curigliano G, ESMO BREAST 2020

Adverse event	Tucatinib combination (*N* = 404) *n* (%)		Placebo combination (*N* = 197) *n* (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	57 (14.1)	105 (53.3)	18 (9.1)
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

tucatinib combination: tucatinib, trastuzumab, and capecitabine. Placebo combination: placebo, trastuzumab, and capecitabine.

Take home message

- Il trattamento di terza linea nel tumore della mammella avanzato HER2 + è rappresentato da tucatinib (TUKYSA) (se il paziente ha già ricevuto il trastuzumab deruxtecan)

- Nello studio HER2Climb la terapia tucatinib-capecitabina e trastuzumab è associata un numero di eventi avversi superiore al braccio di controllo (trastuzumab-capecitabina-placebo). Gli eventi avversi più frequenti sono rappresentati da tossicità gastrointestinale

- In particolare la diarrea di qualsiasi grado viene osservata nell'82% dei pazienti con una diarrea > o = al grado 3 in un 13% di pazienti.

- Il profilo di tossicità riportato richiede un attenta valutazione del paziente.


Grazie