bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

HIGHLIGHTS – MBC
HER2+/HER2-low

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Disclosures

- PF Roche
- PF Gilead
- PF Novartis
- PF Pfizer
- PF Menarini
- PF Astrazeneca
- PF MSD

HER2+

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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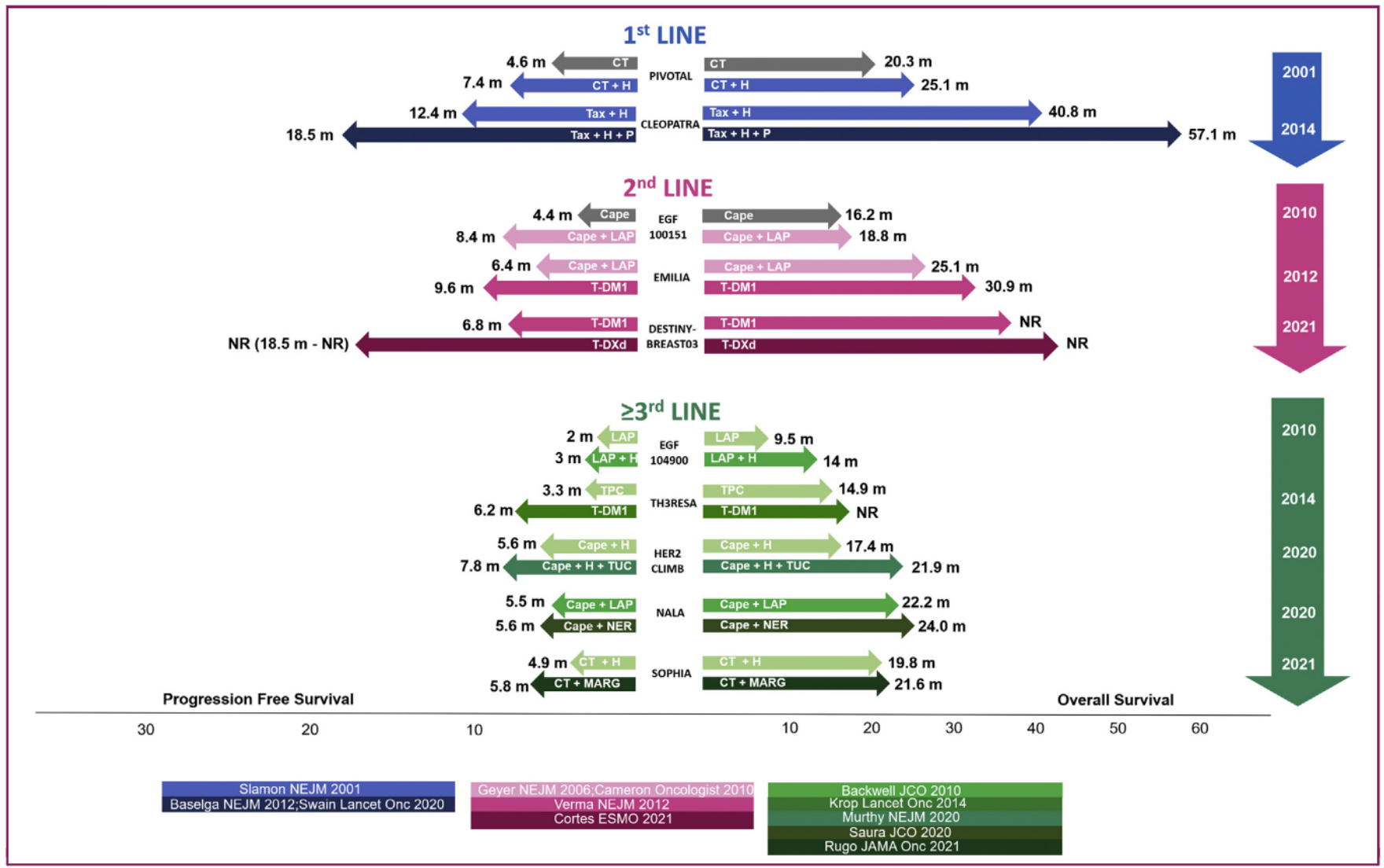
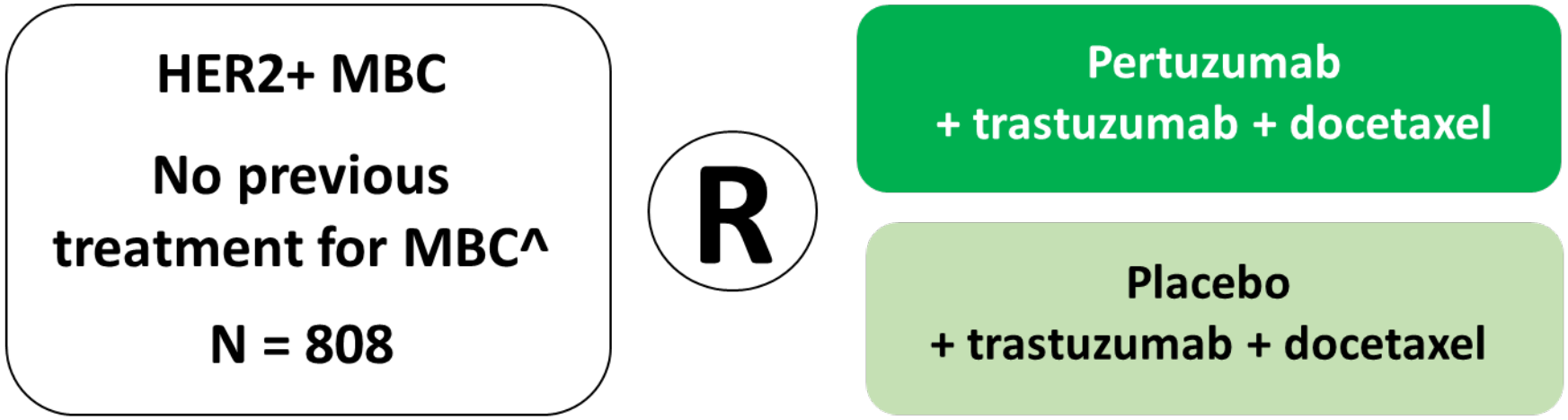


CRYSTALLIZED 1st line scenario - TRASTUZUMAB+PERTUZUMAB

CLEOPATRA



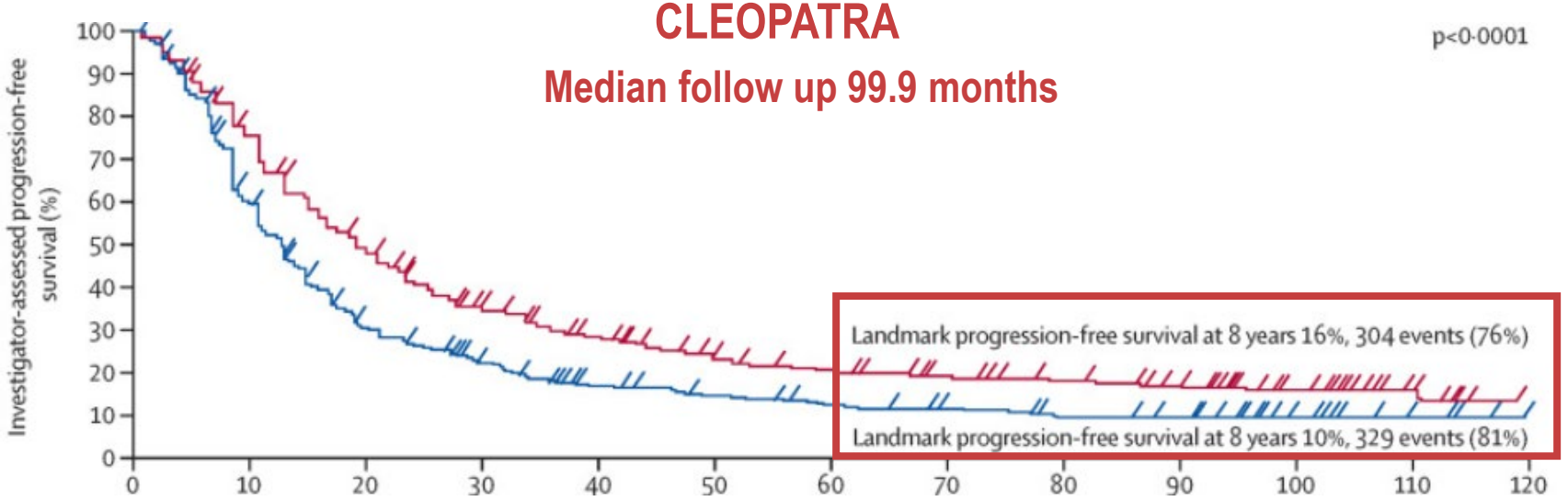
^ Previous CT+/-trastuzumab in the curative setting allowed if completed >12 months before randomization

CRYSTALLIZED 1st line scenario - TRASTUZUMAB+PERTUZUMAB

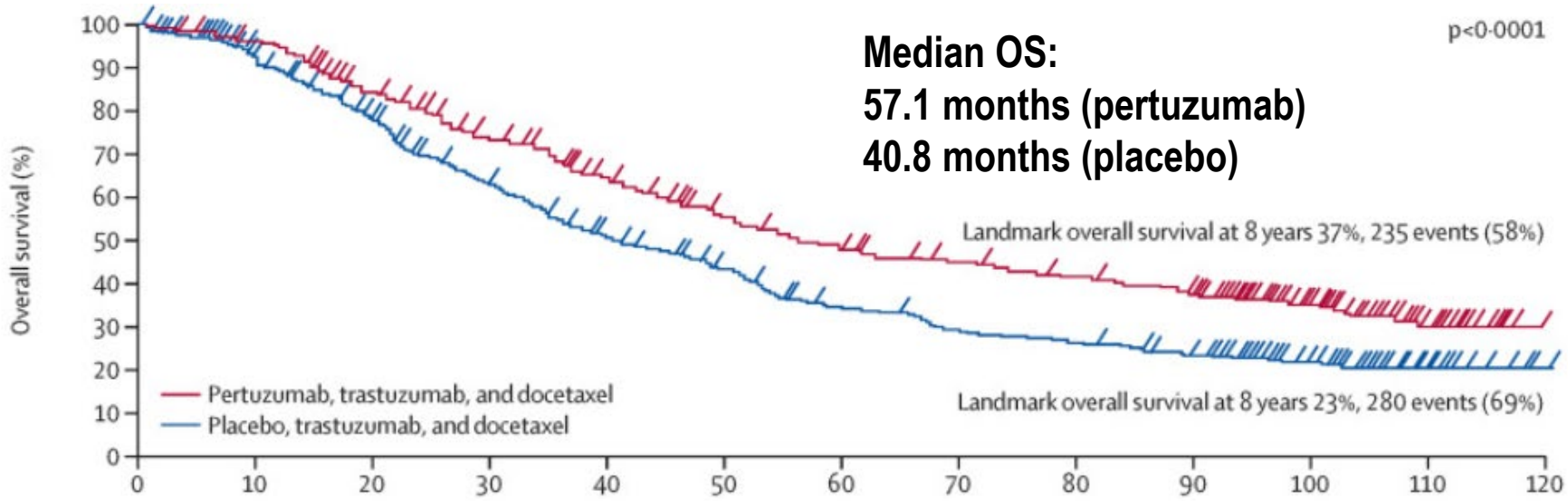
CLEOPATRA

Median follow up 99.9 months

PFS (final)



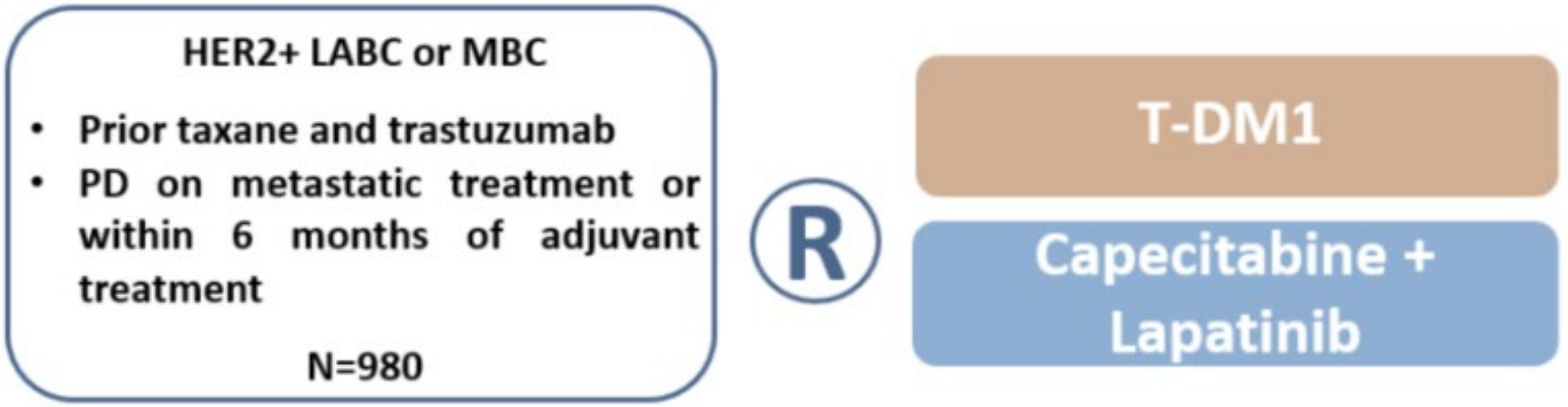
OS (final)



Baselga et al, NEJM 2012; Swain et al Lancet Oncol 2020

HISTORICAL 2nd line scenario – TDM1

EMILIA

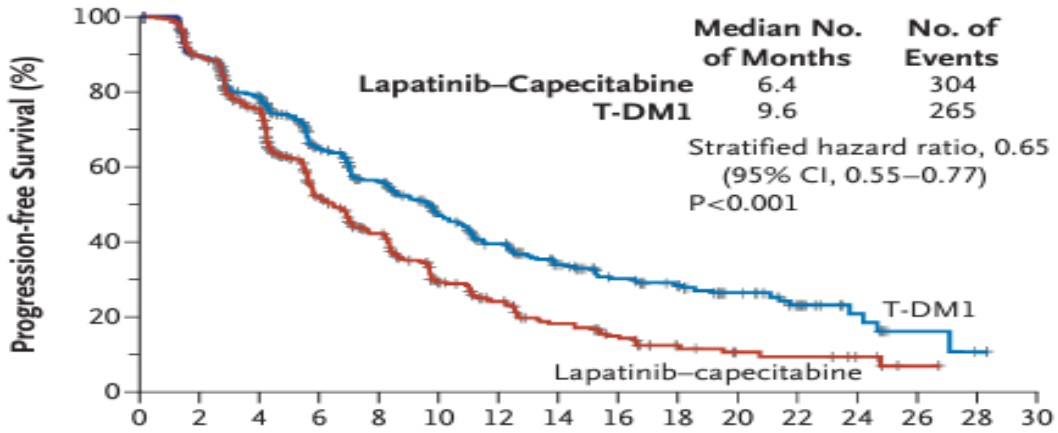


Verma et al NEJM 2012 ;Dieras et al, Lancet Oncoil 2017; Guarneri V, SABCS 2023 GS Discussion

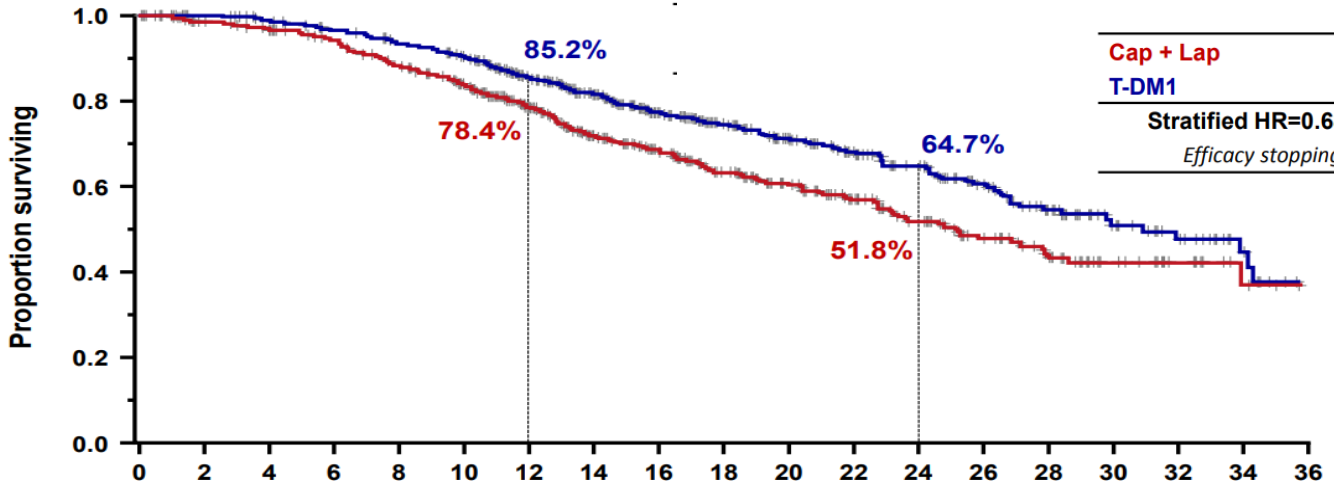
HISTORICAL 2nd line scenario – TDM1

EMILIA

PFS (primary analysis)



OS (confirmatory analysis)



	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

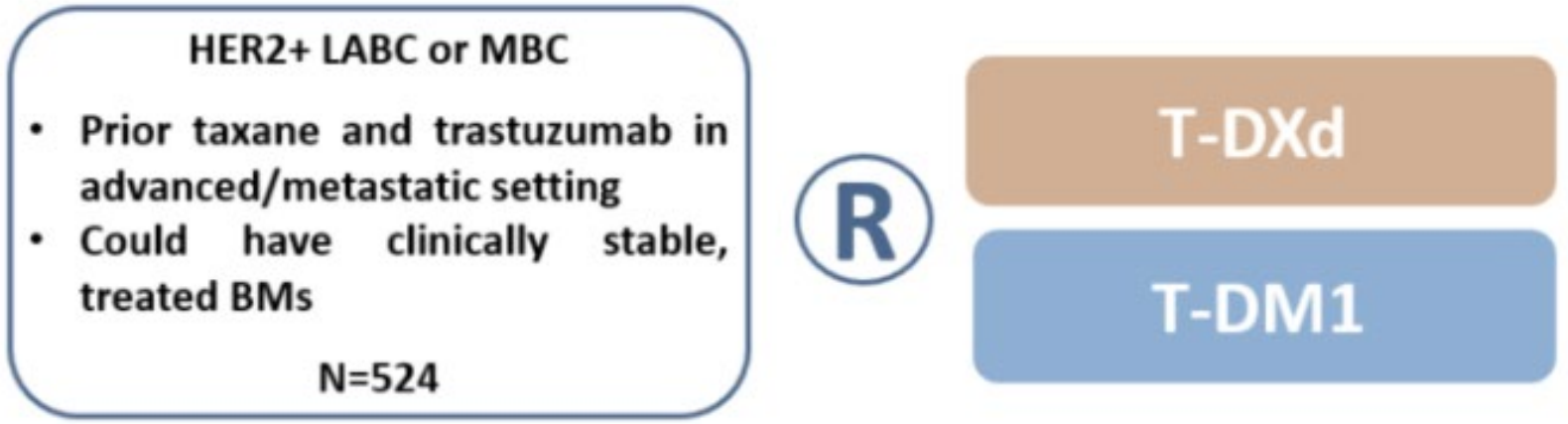
Efficacy stopping boundary P=0.0037 or HR=0.727

Crossover from control arm to TDM1 arm = 27%

Verma et al NEJM 2012 ;Dieras et al, Lancet Oncoil 2017; Guarneri V, SABCS 2023 GS Discussion

CONTEMPORARY 2nd line scenario – TDXd

DESTINY-BREAST03



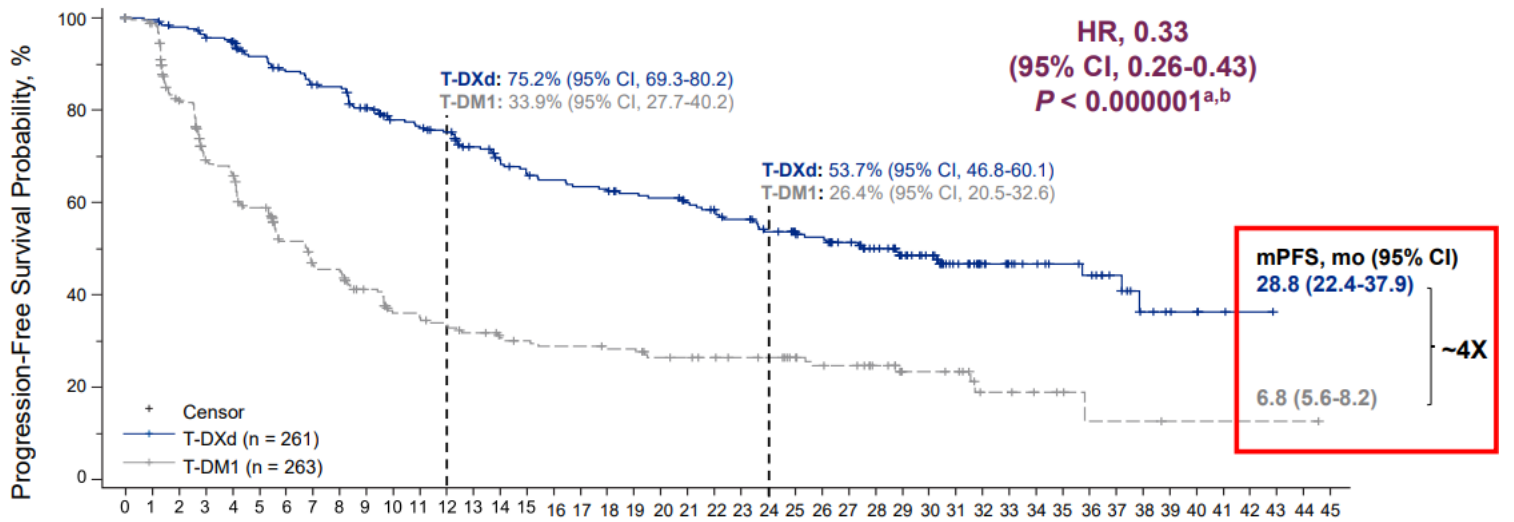
Primary endpoint: PFS as determined by blinded independent central review

In pts treated with TDXD:
- **62% prior pertuzumab**
- 41% 1 prior Tx for MBC

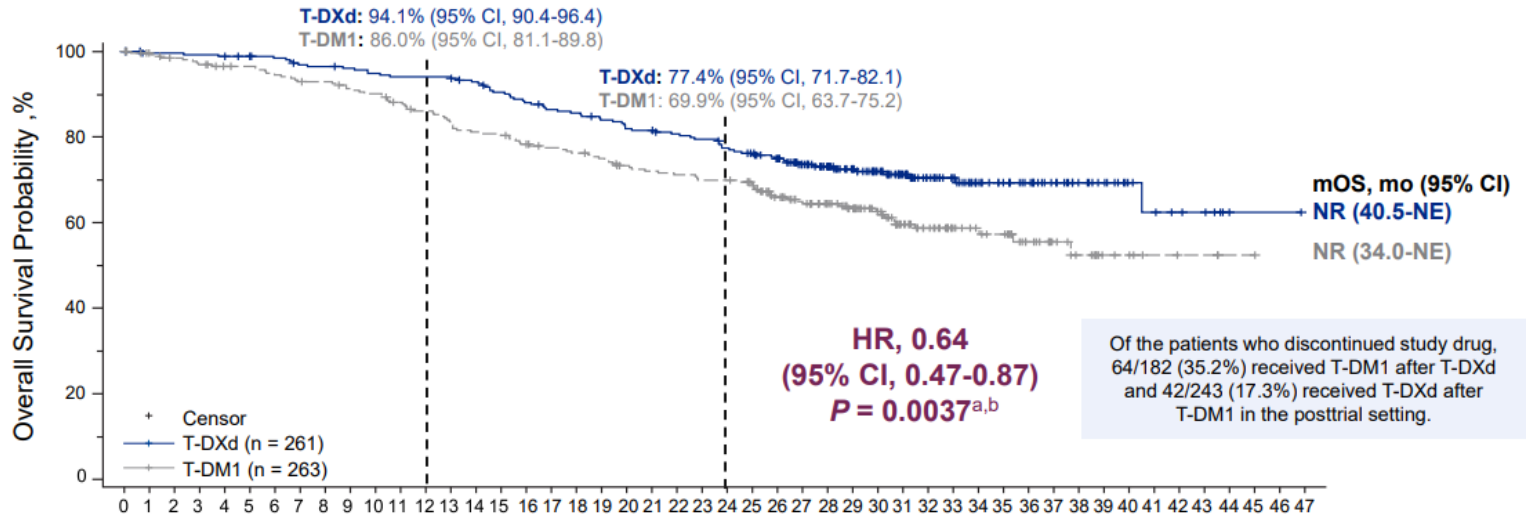
CONTEMPORARY 2nd line scenario – TDXd

DESTINY-BREAST03

PFS (update)



OS (update)

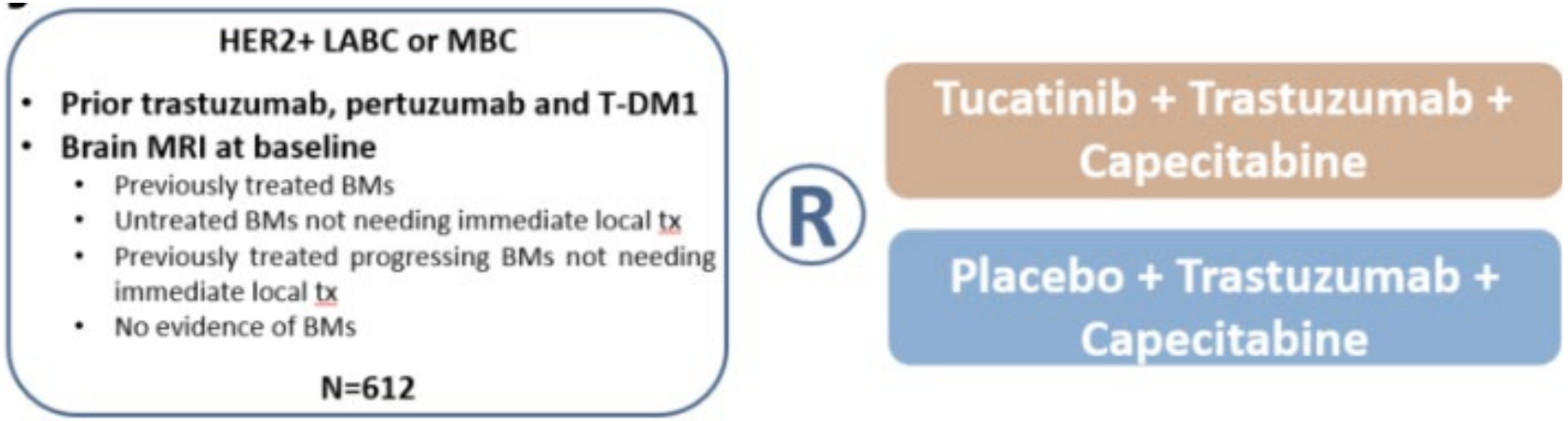


Of the patients who discontinued study drug, 64/182 (35.2%) received T-DM1 after T-DXd and 42/243 (17.3%) received T-DXd after T-DM1 in the posttrial setting.

Cortes J et al, ESMO 2021, NEJM 2022; Hurvitz Lancet Oncol 2023

CONTEMPORARY 3rd line scenario – TUCATINIB

HER2CLIMB



Primary endpoint: PFS as determined by blinded independent central review in the first 480 patients who underwent randomization

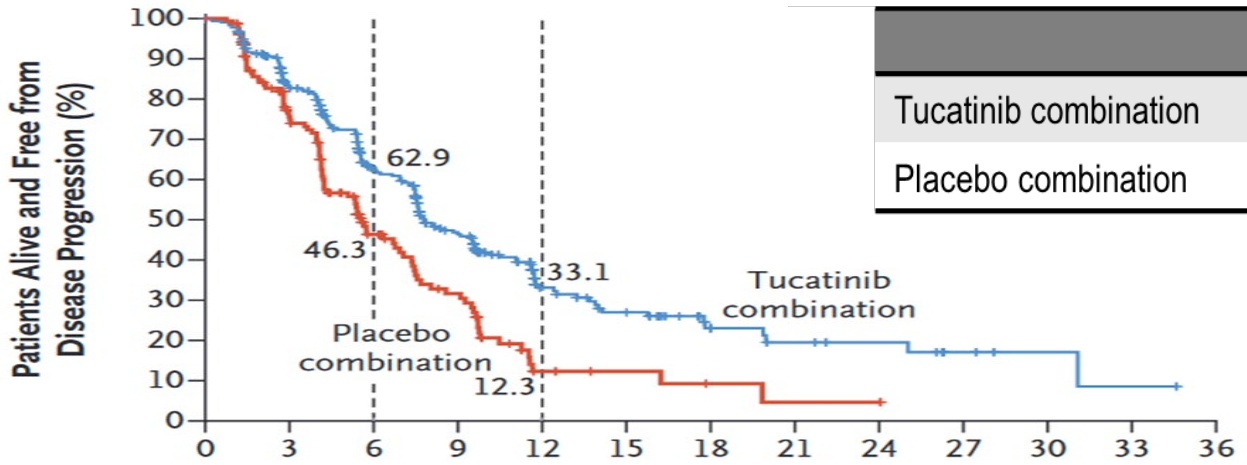
(The size of the trial population was later increased to approximately 600 patients to ensure sufficient power to show a progression-free survival benefit among the patients with brain metastases.)

- median previous lines of Tx: 4
- 100% received trast, pert and T-DM1
- CNS disease: 48% (total population, tucatinib arm); ~ 30% active BMs

CONTEMPORARY 3rd line scenario – TUCATINIB

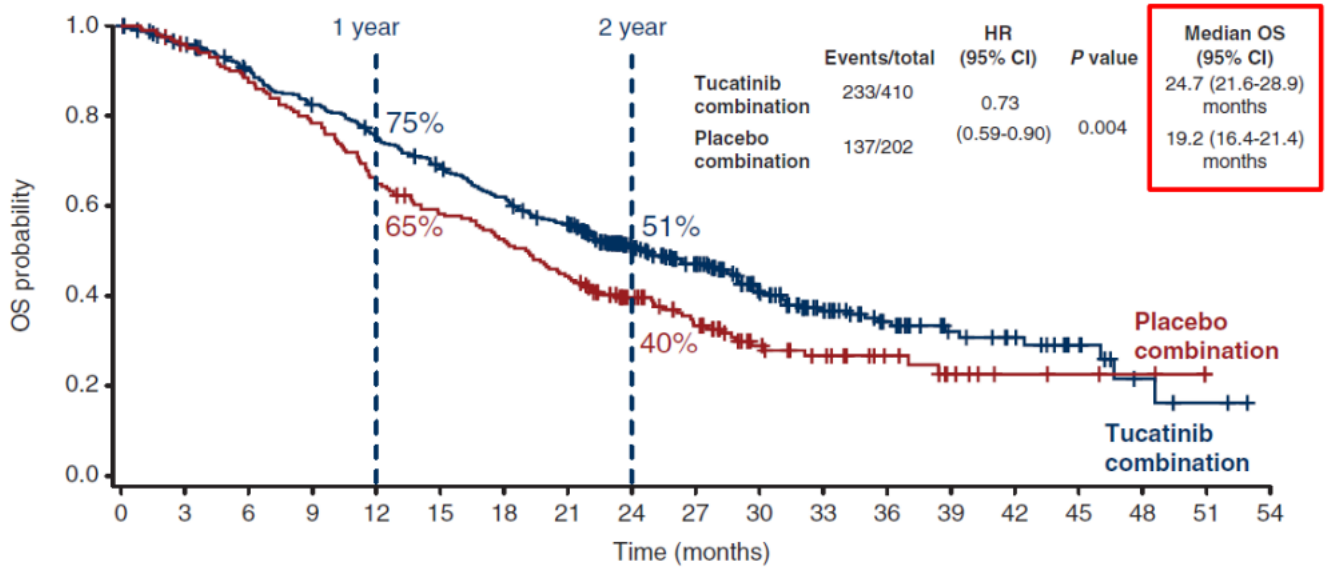
HER2CLIMB

PFS (primary analysis)



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

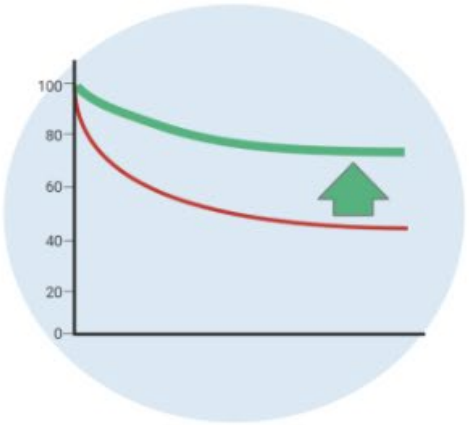
OS (update)



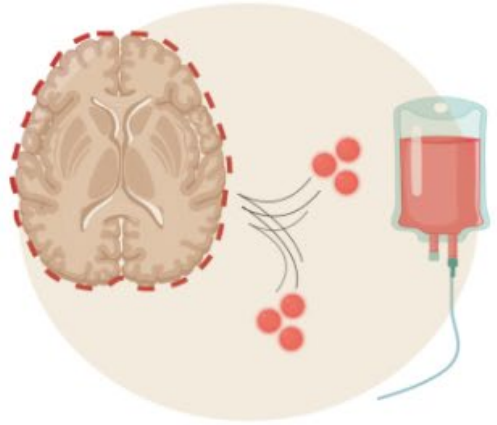
Murthy RK, et al. N Engl J Med 2020; Curigliano et al, Ann Oncol 2022

Brain mets in HER2+ disease

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



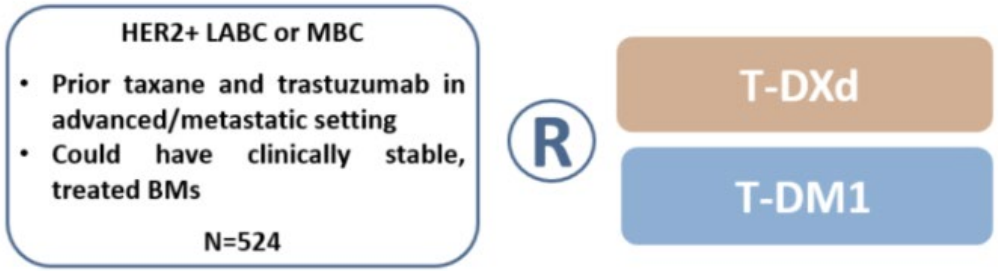
Prolonged survival and better extra-CNS disease control
with contemporary regimens for eBC and mBC



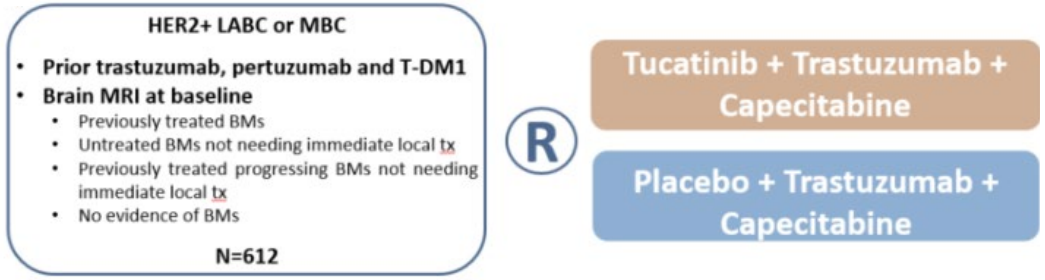
CNS as a sanctuary site for metastases in eBC
inadequate drug penetration of anti-HER2 agents into the brain parenchyma through the BBB

Are the DB-04 and HER2CLIMB trials reliable in defining TDXd and Tuc efficacy in BMs?

DESTINY-BREAST03



HER2CLIMB



Brain metastases	
N=62 (23.8%)	N=198 (48.3%)
Stable BMs	
100%	40.4%
Active BMs	
(treated and progressing, untreated)	
0%	59.6%

Cortes et al, NEJM 2022; Lin et al, JCO 2020

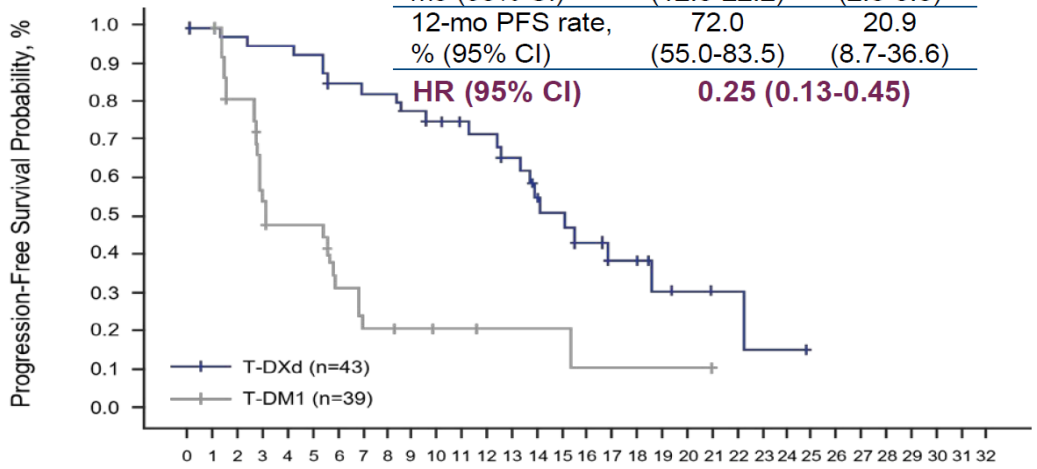
T-DXd and Tucatinib activity/efficacy in pts with STABLE BMs

T-DXd

DB-03

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)	

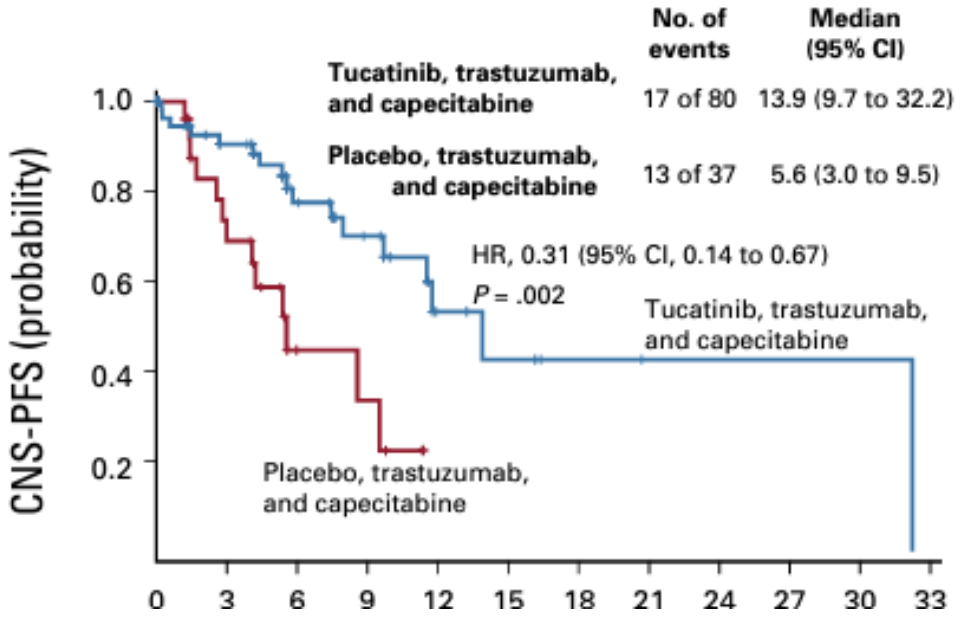


Intracranial response

	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)

TUCATINIB

HER2CLIMB



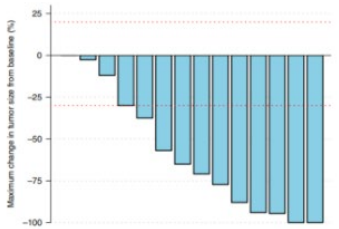
	Median survival Tucatinib	Median survival Placebo	HR (95% CI)
CNS-PFS stable BM	13.9	5.6	0.41 (0.19-0.85)
OS stable BM	21.6	16.4	0.70 (0.42-1.16)

Hurvitz et al, SABCS 2021; Curigliano et al, Ann Onc 2021; Lin et al, JCO 2020

T-DXd and Tucatinib activity/efficacy in pts with ACTIVE BMs

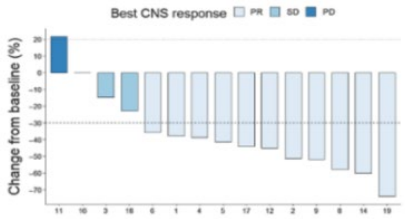
T-DXd

TUXEDO-1 study (n=15)



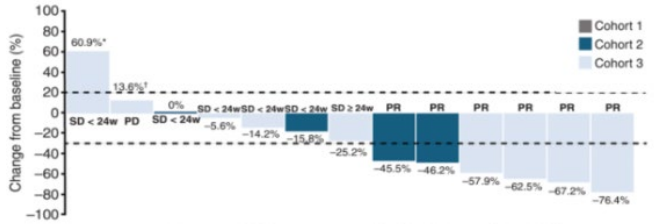
Intracranial RR = 73.3%

DFCI/MDACC/Duke (n=15*)
*15/17 with evaluable intracranial RR



Intracranial RR = 73%

DEBBRAH (n=13*)
*active BM cohorts (2 and 3)



Overall intracranial RR = 46.2%
(asymptomatic untreated + progressing BMs)

MADRID 2023 ESMO congress

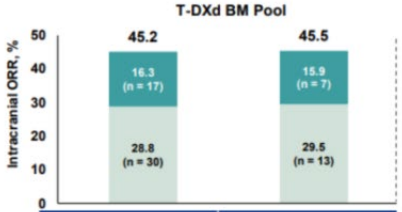
A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

Presentation 3770

Sara A. Hurvitz[1], Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaque, Anton Egorov, Fabrice André

On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

In T-DXd pool, 29.7% of pts had untreated/active BMs

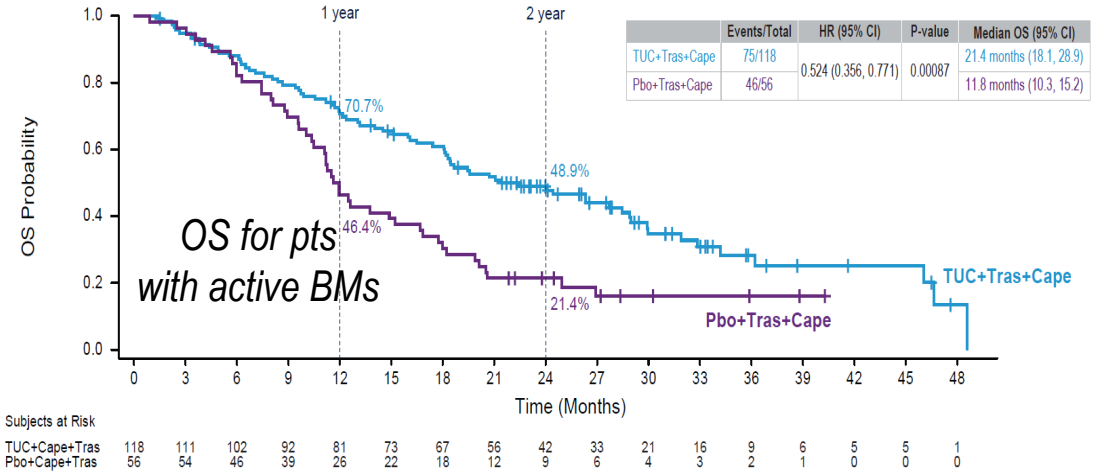


	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)
Best overall IC response, n (%)		
Stable disease	48 (46.2)	15 (34.1)
Progressive disease	3 (2.9)	1 (2.3)
Not evaluable/Missing	6 (5.8)	8 (18.2)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)

TUCATINIB

HER2CLIMB

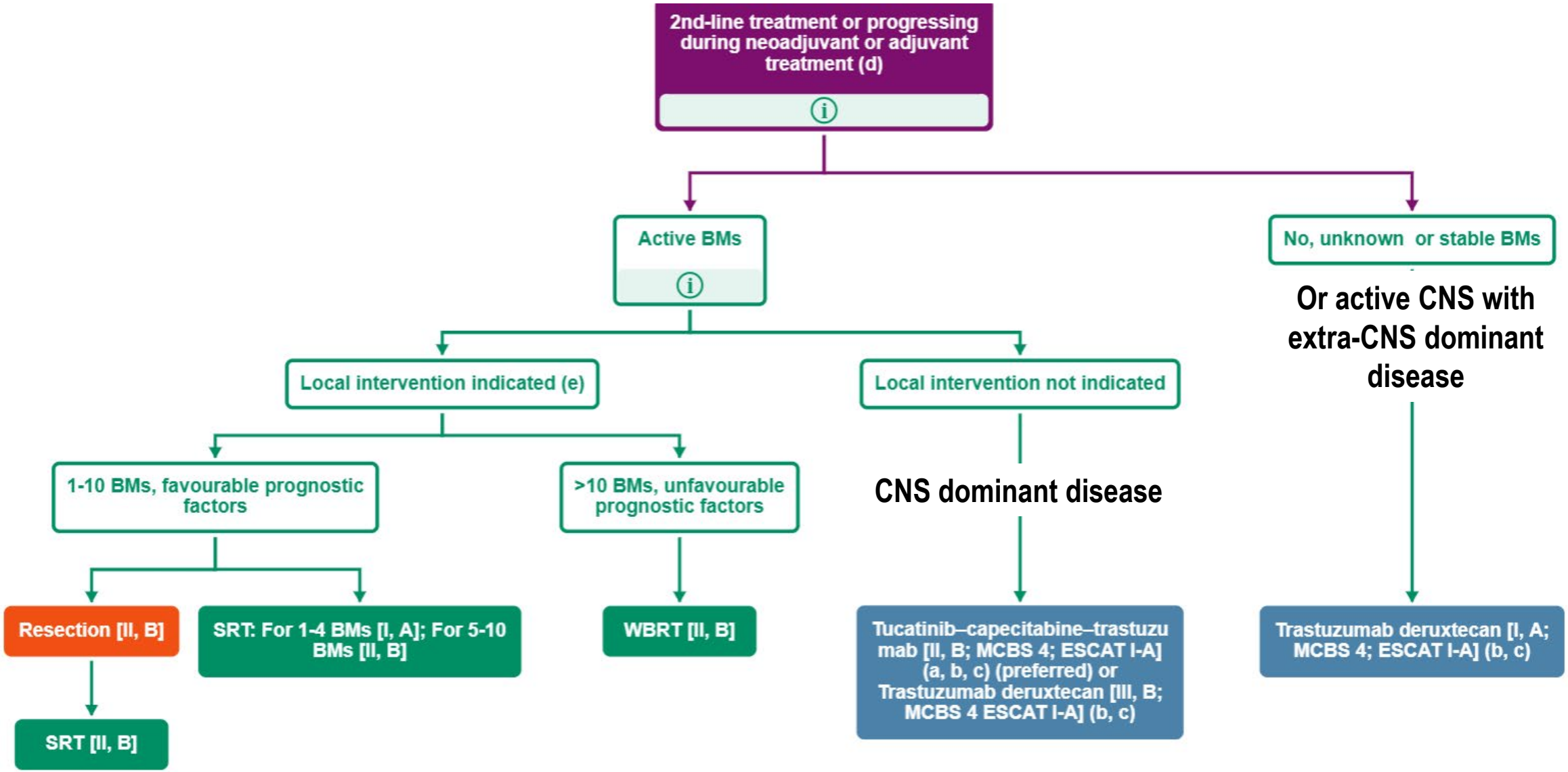
	Median survival Tucatinib	Median survival Placebo	HR (95% CI)
CNS-PFS active BM	**9.6**	**4.0**	**0.34 (0.22-0.54)**
OS active BM	**21.4**	**11.8**	**0.52 (0.36-0.77)**



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

Bartsh Nature Med 2022; Kabraji CCR 2023; Garcia Neuro-Oncol 2023; Hurvitz ESMO 2023; Lin Jama Oncol 2023

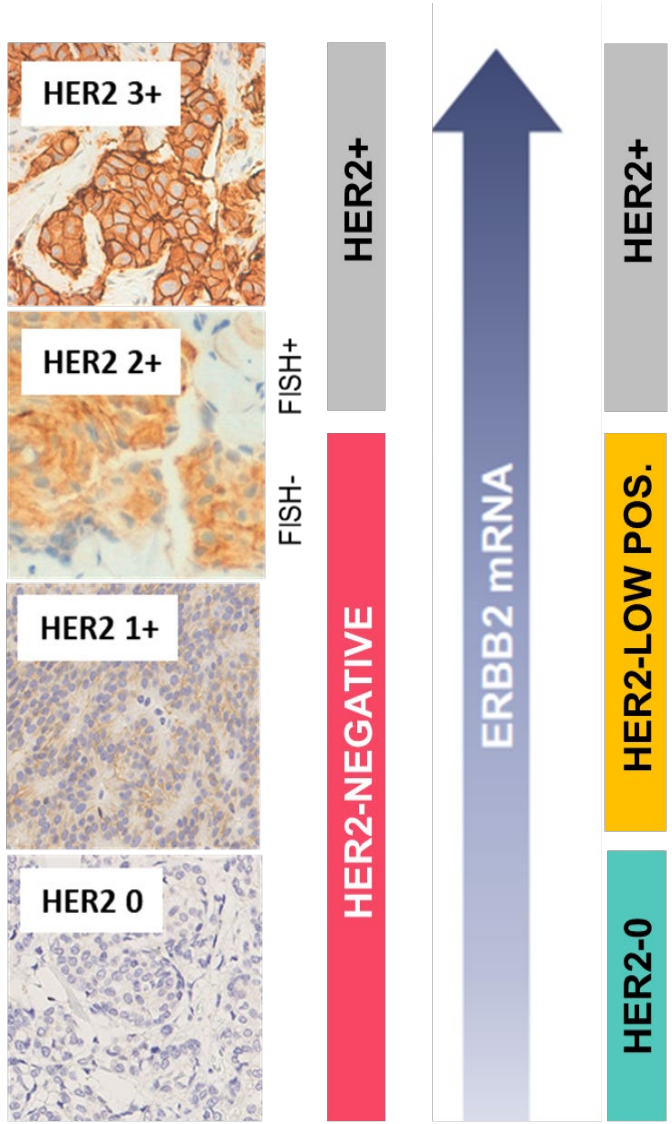
Treatment algorithm



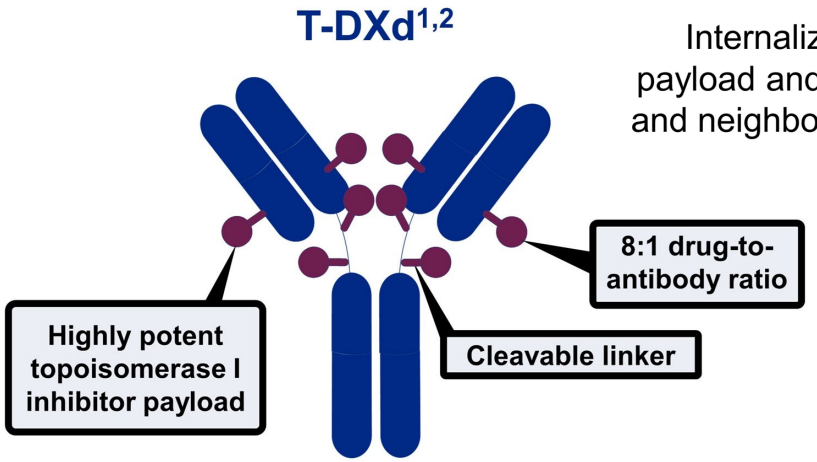
Gennari et al, Ann Oncol 2021; ESMO living guidelines

HER2-low

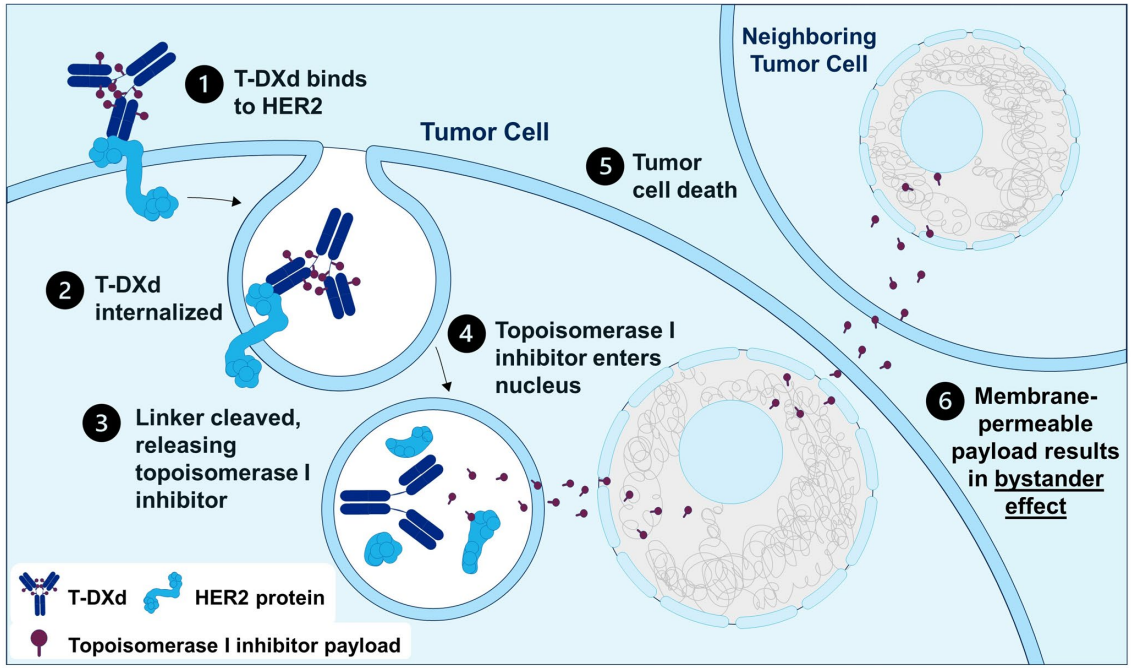
HER2-low BC



Courtesy of *Dr M. Lo Mele, MD*, Pathology Unit Padova Hospital, Italy



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



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

Destiny-Breast04 trial

DESTINY-BREAST04

HER2+ LABC or MBC

- **HER2-low MBC**
- **1-2 prior CT for MBC**
- **HR+ considered endocrine-refractory**

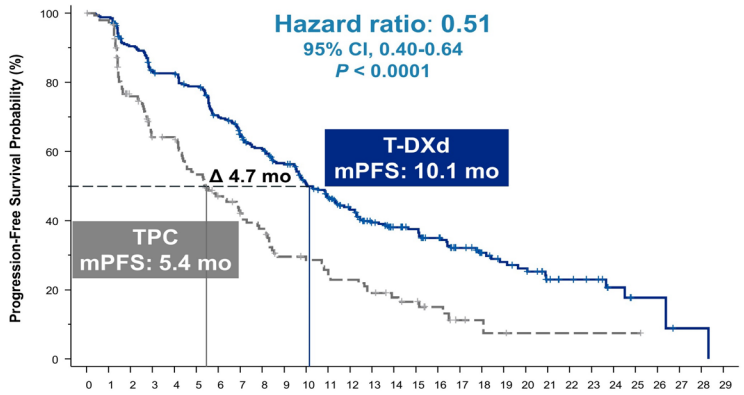
R

Trastuzumab Deruxtecan

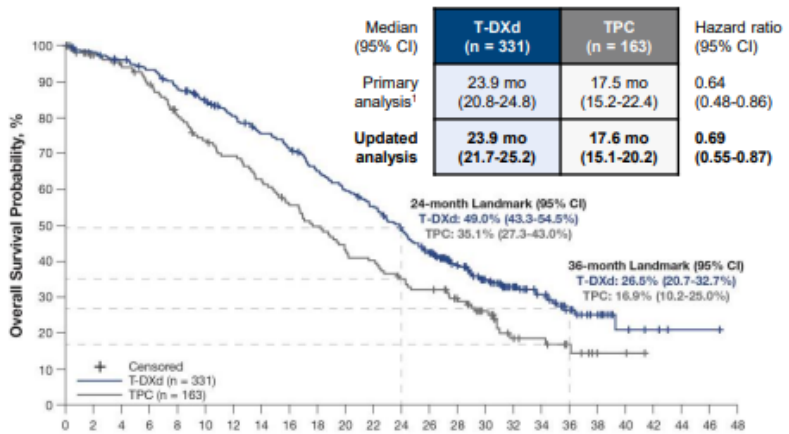
TPC

- Mostly HR+ (~ 90%)
- ~90% of HR+ pre-treated with CDK 4/6i

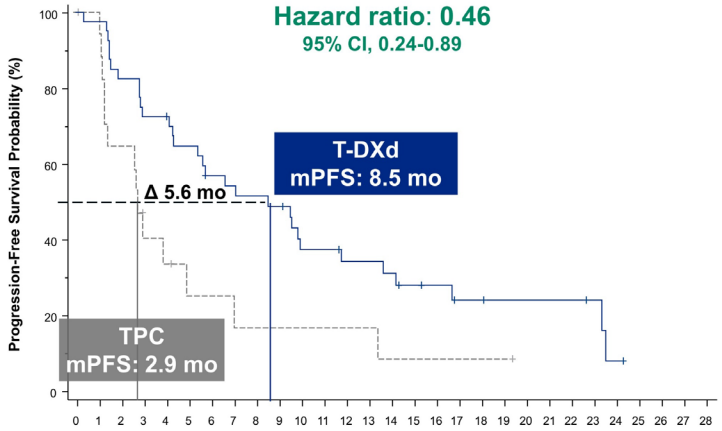
PFS - HR+



OS - HR+

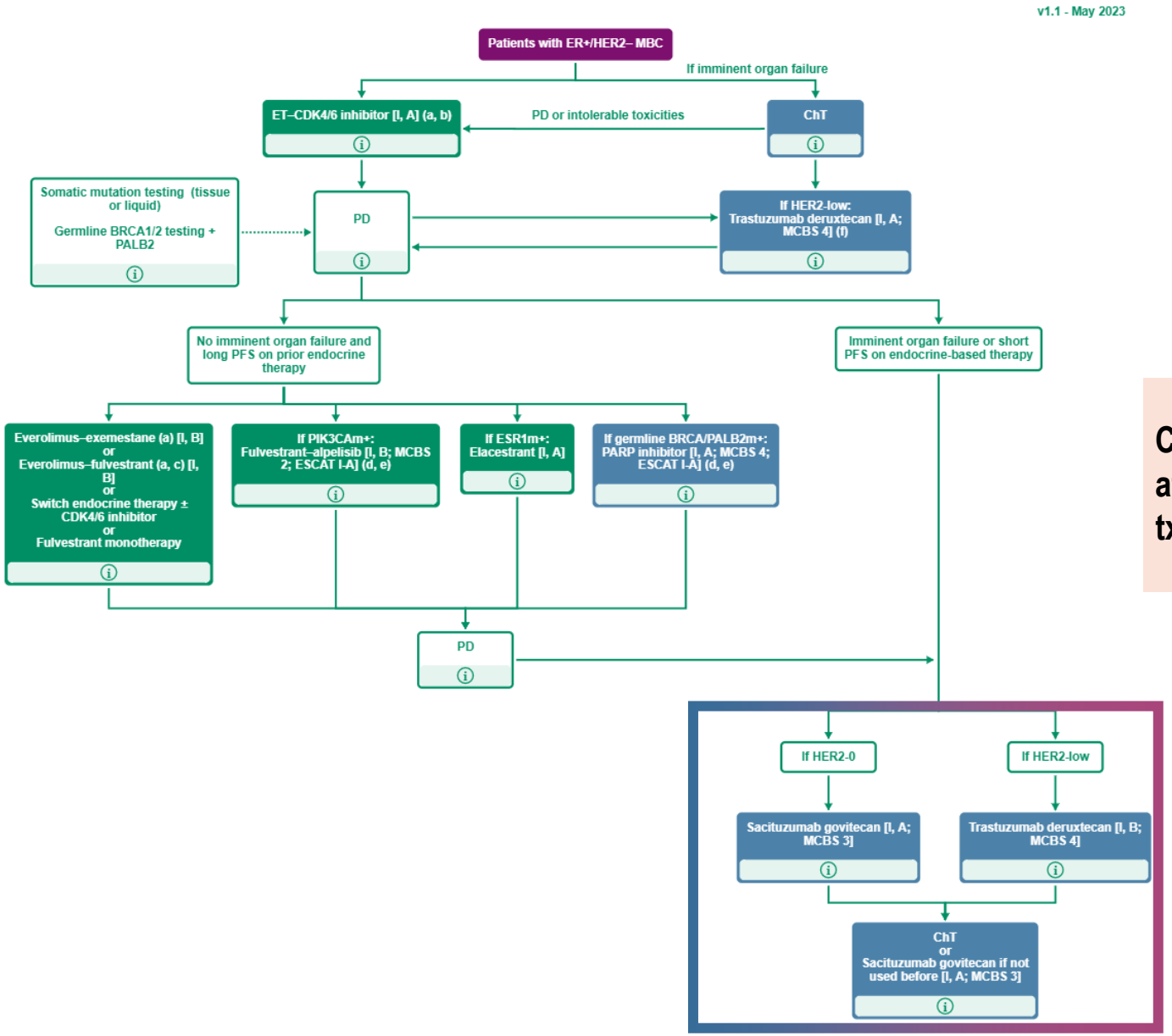


PFS – HR-



Modi S et al., ASCO 2022, NEJM 2022, ESMO 2023

T-DXd in HR+/HER2-low MBC



Consider CT-based options after exhaustion of ET-based tx or expected benefit from ET.

ESMO living guidelines

Competing scenario: TROPICS-02 trial

Rugo et al, JCO 2022;
Rugo et al, Lancet Oncol 2023;
Rugo et al, ESMO 2022

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

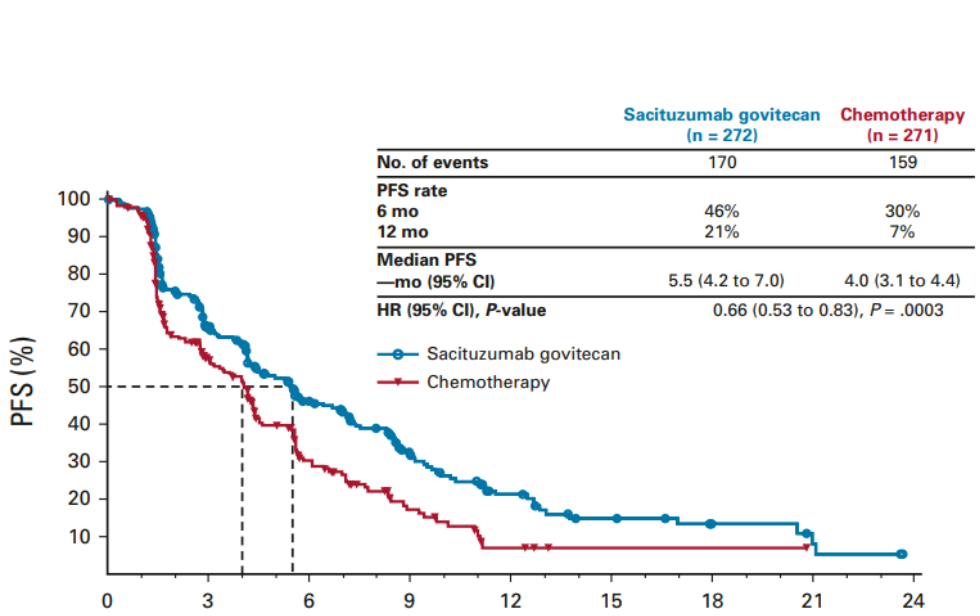
Endpoints

Primary
- PFS by BICR

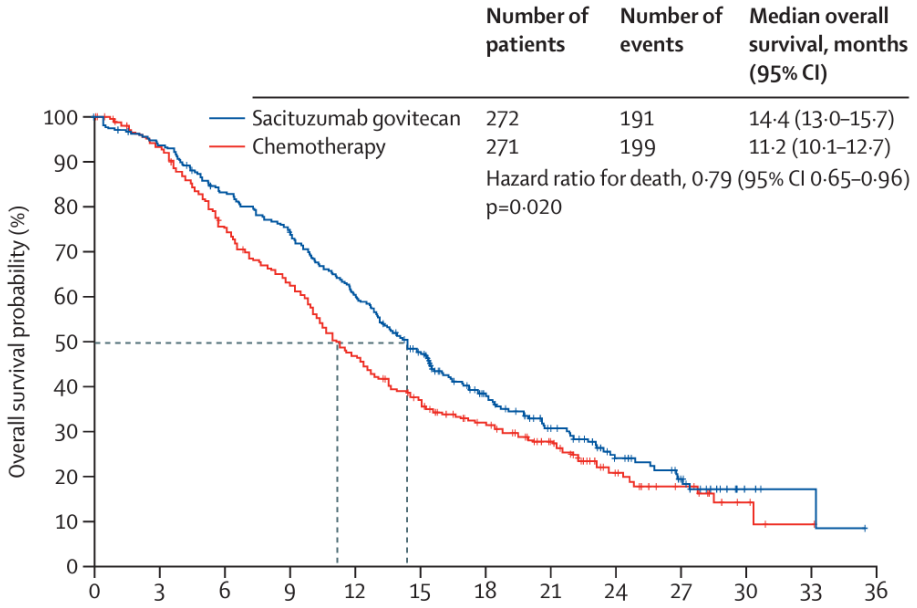
Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

SG arm:
- Median **prior tx lines**: 3 (2, 38%; ≥3, 58%)
- **Prior CDK 4/6i use**: ≤12 mos 58%



	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46%	30%
12 mo	21%	7%
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	



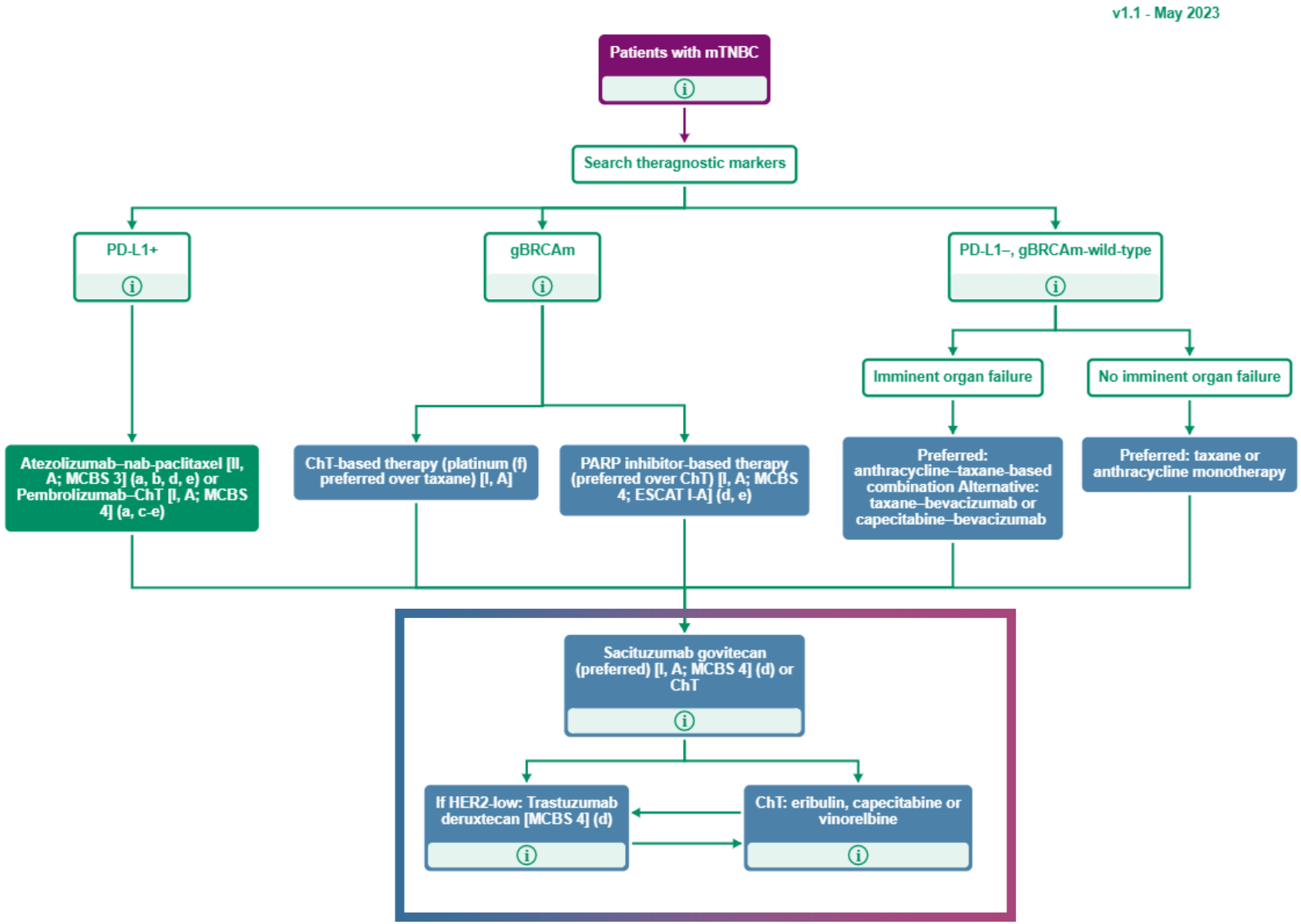
	Number of patients	Number of events	Median overall survival, months (95% CI)
Sacituzumab govitecan	272	191	14·4 (13·0–15·7)
Chemotherapy	271	199	11·2 (10·1–12·7)

Hazard ratio for death, 0·79 (95% CI 0·65–0·96)
p=0·020

TROPIC02 trial: <u>more heavily pre-treated</u> population compared to DB04 trial.

SG efficacy confirmed regardless of HER2 IHC groups → confirmed also in HER2-low BC

T-DXd in HR-/HER2-low MBC

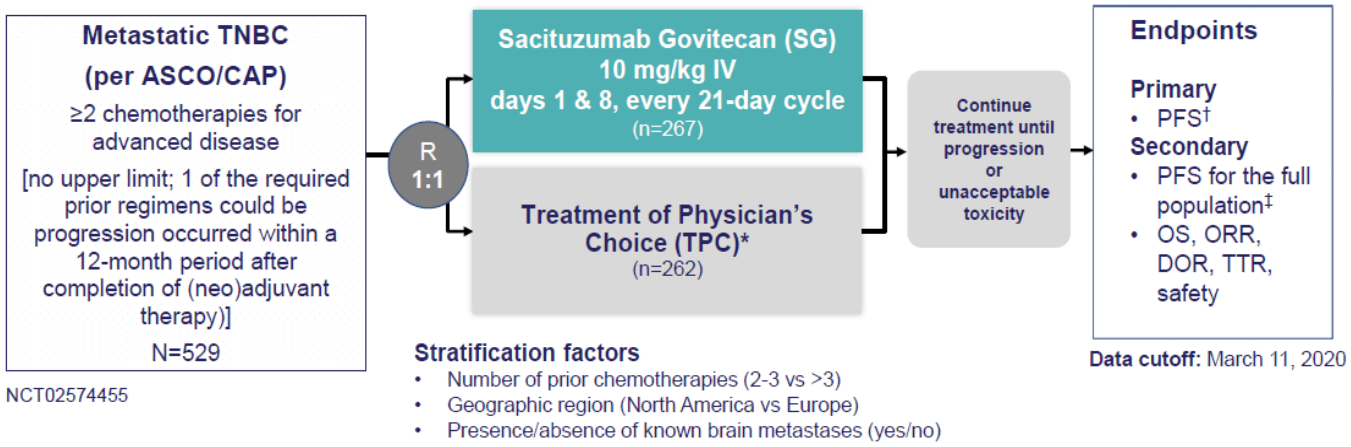


ADC positioning: ≥ 2nd line

ESMO living guidelines

Competing scenario: ASCENT trial

Bardia A et al, ESMO 2020, NEJM 2021; Hurvitz et al, SABCS 2020

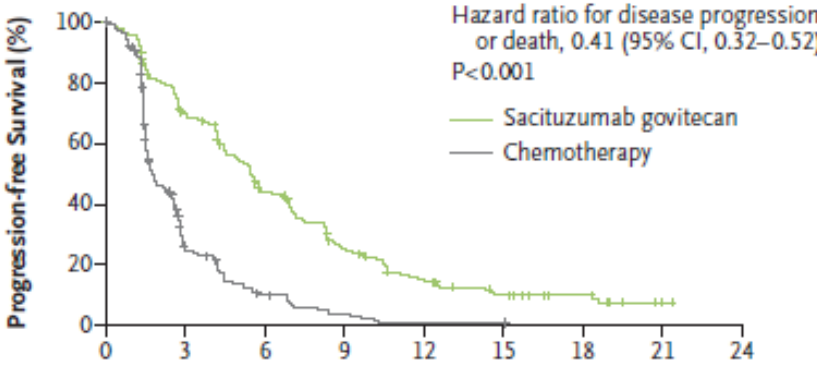


NCT02574455

- TNBC at initial diagnosis ≈70%
- Median anticancer regimens: 4 (2-17)
- **29-26% previously treated with PD-1/PD-L1 inhibitors**
- **17-18% previously treated with PARP inhibitors**

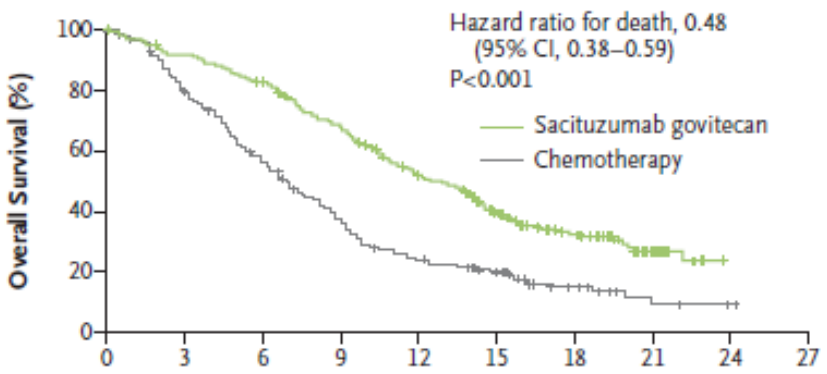
Without BMs

	No. of Patients	No. of Events	Median Progression-free Survival *mo (95% CI)*
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)



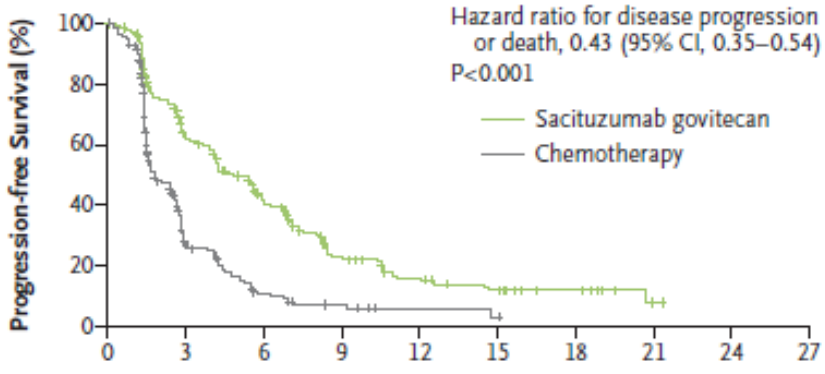
Without BMs

	No. of Patients	No. of Events	Median Overall Survival *mo (95% CI)*
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)



Full population

	No. of Patients	No. of Events	Median Progression-free Survival *mo (95% CI)*
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)



Remarks

- **HER2+: the Cleopatra, DB03 and H2C trials set trastuzumab-pertuzumab-taxane, T-DXd and tucatininb-trastuzumab-capecitabine as the standard 1st, 2nd and 3rd line tx**
  - The only setting were tucatininb-based tx may be prioritized over T-DXd is represented by pts with ACTIVE BMs and CNS-dominant disease

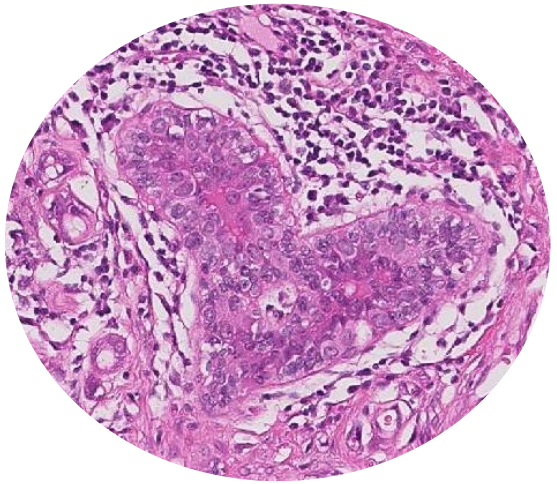
- **HER2-low MBC represents an operational entity** → guidance for determining access to T-DXd

- **T-DXd** currently represents a viable option **for HER2-low MBC pre-treated with 1-2 CT lines**
  - HR+/HER2-: after exhaustion of ET-based lines/expected benefit
  - TNBC: after exhaustion of targeted options (ICI and PARP-i)

- **T-DXd positioning partially overlap with SG both in HR+ and TNBC**:
  - HR+/HER2-: T-DXd to be prioritized over SG
  - TNBC: SG to be prioritized over T-DXd

Grazie

Federica Miglietta



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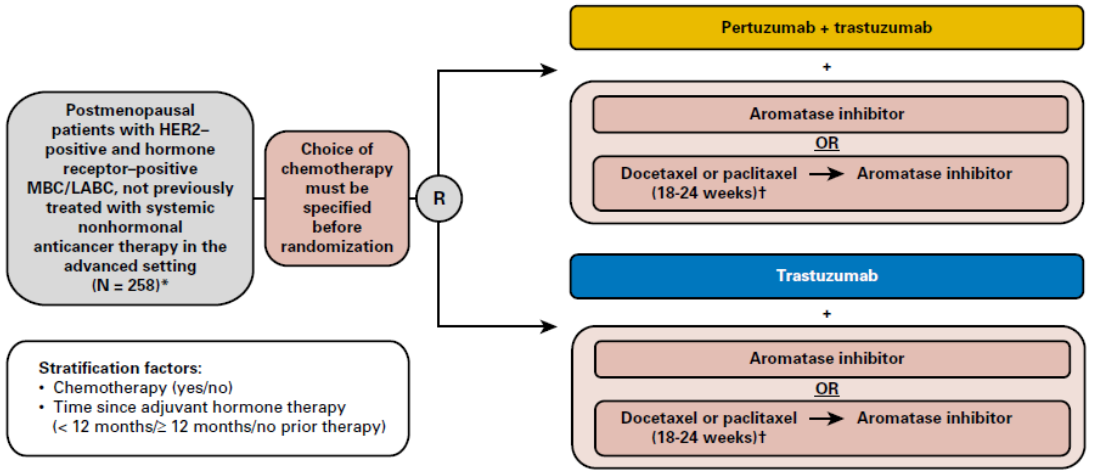
bjclub breast Journal Club

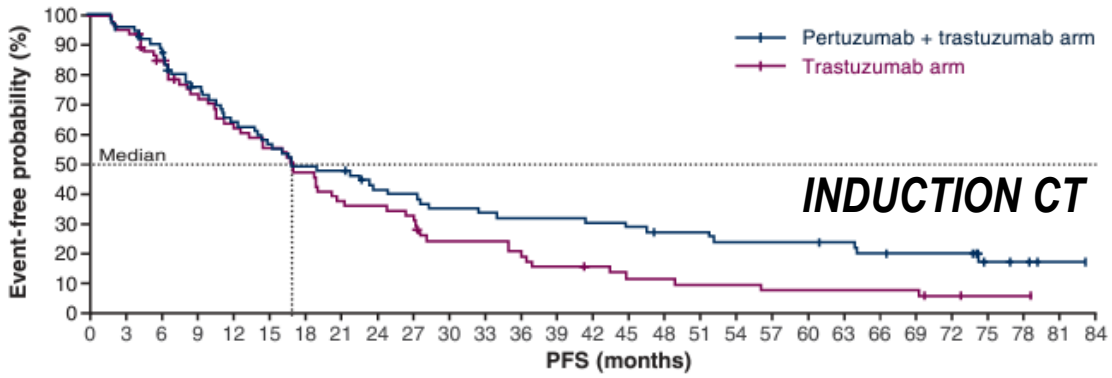
L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

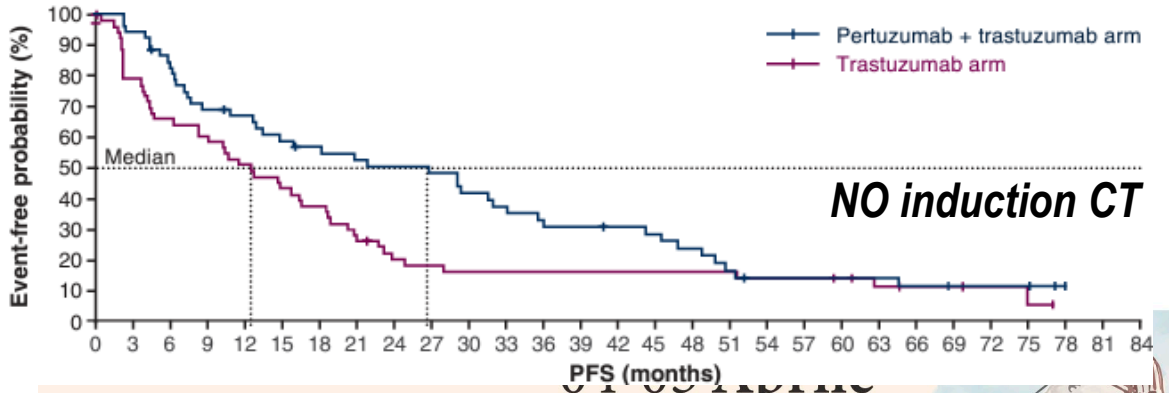
04-05 **Aprile**
2024 **Padova**

CRYSTALLIZED 1st line scenario – what about ET?

PERTAIN







Rimawi et al, JCO 2018; Arpino et al, CCR 2023

Is there a role for the association of Tucatinib + TDM1?

HER2CLIMB-02

HER2+ LABC or MBC

- **Prior trastuzumab and taxane**
- **Previously treated stable, progressing or untreated BMs (not requiring immediate local tx)**

N=612

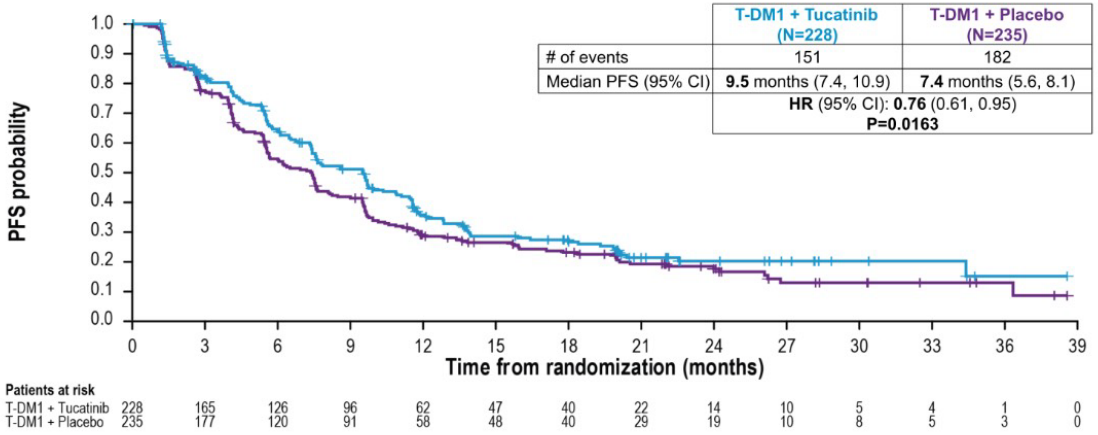
R

Tucatinib + TDM1

Placebo + TDM1

- Mostly 2L
- ~90% pertuzumab pre-treated
- 40% BMs

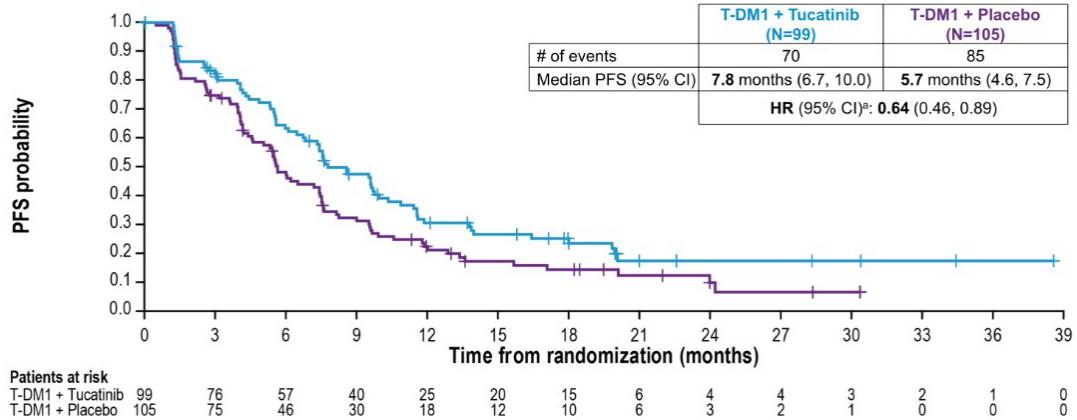
Progression-Free Survival



	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	

HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

PFS in Patients with Brain Metastases



	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI)[a]: **0.64** (0.46, 0.89)	

a The outcome was not formally tested.
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Hurvitz et al, SABCS 2023