IL CARCINOMA MAMMAMARIO METASTATICO HER2+

Federica Miglietta

Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche – Università di Padova
Oncologia 2 -Istituto Oncologico Veneto - IRCCS

CONFLICT OF INTEREST

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

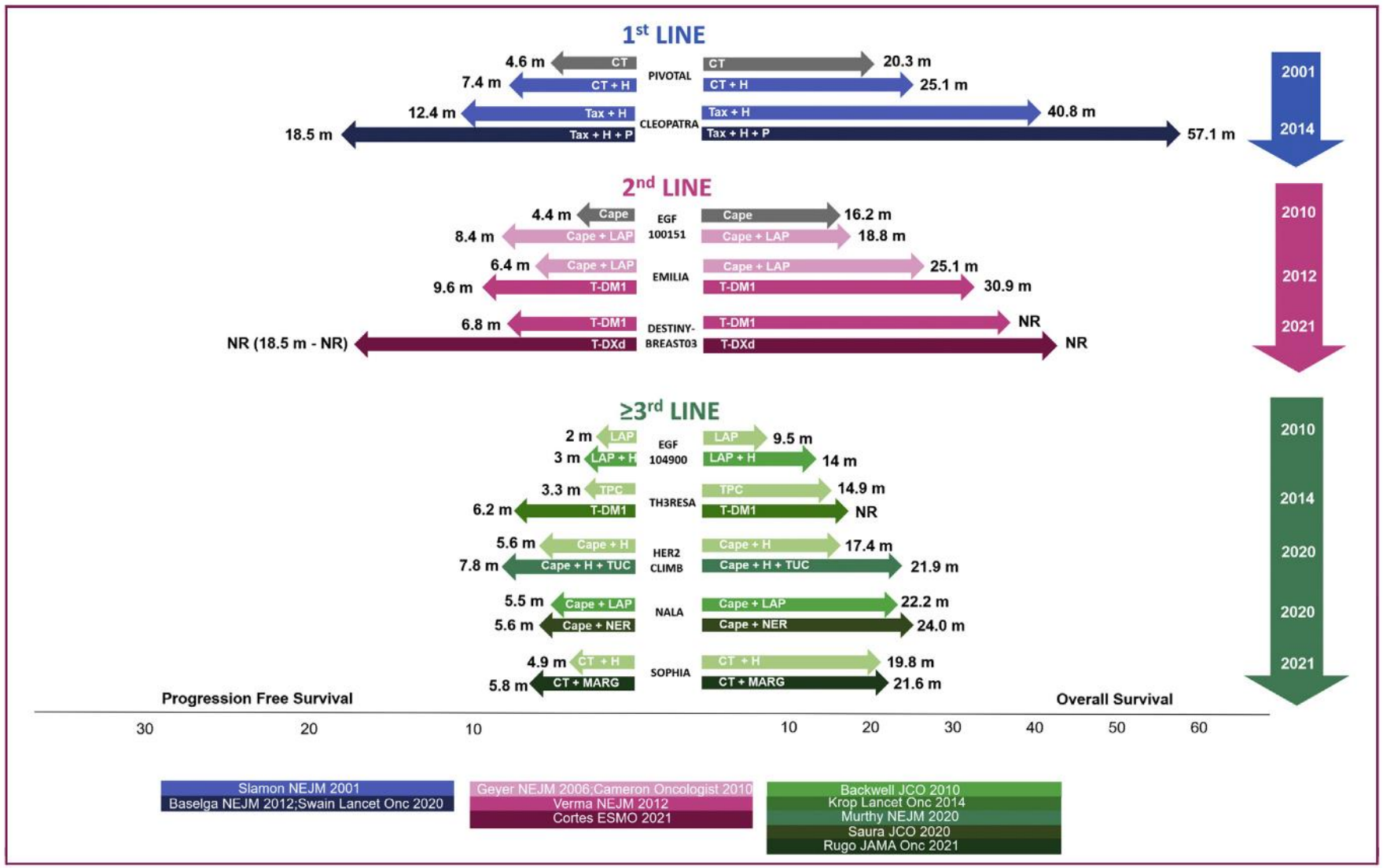
REVIEW

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

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

F. Miglietta[1], M. Bottosso[1], G. Griguolo[1,2], M. V. Dieci[1,2] & V. Guarneri[1,2*]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova; [2]Division of Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy



ATTRITION RATE IN HER2+ MBC

	First-to-second, % (95%CI)	Second-to-third, % (95%CI)
Overall	9.0 (7.9-10.1)	14.0 (12.4-15.6)
HR+/HER2-	8.5 (7.9-9.9)	13.0 (11.5-15.2)
HER2+	**7.1 (5.1-9.1)**	**13.0 (9.8-16.1)**
TNBC	13.0 (8.0-17.9)	22.7 (15.6-29.9)

Montemurro F et al., ESMO Breast Cancer 2022

CRYSTALLIZED 1st line scenario - TRASTUZUMAB+PERTUZUMAB

CLEOPATRA

HER2+ MBC

- **NO prior treatment for MBC***

N=808

R

PERTUZUMAB
+ trastuzumab + docetaxel

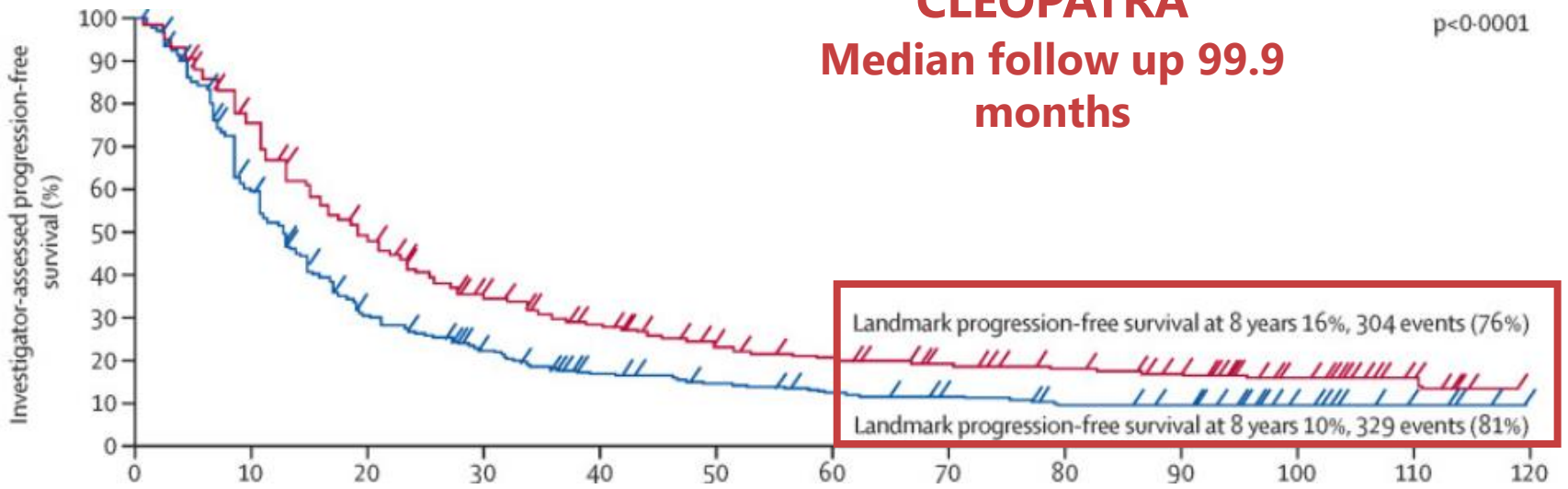
Placebo
+ trastuzumab + docetaxel

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

CRYSTALLIZED 1st line scenario - TRASTUZUMAB+PERTUZUMAB

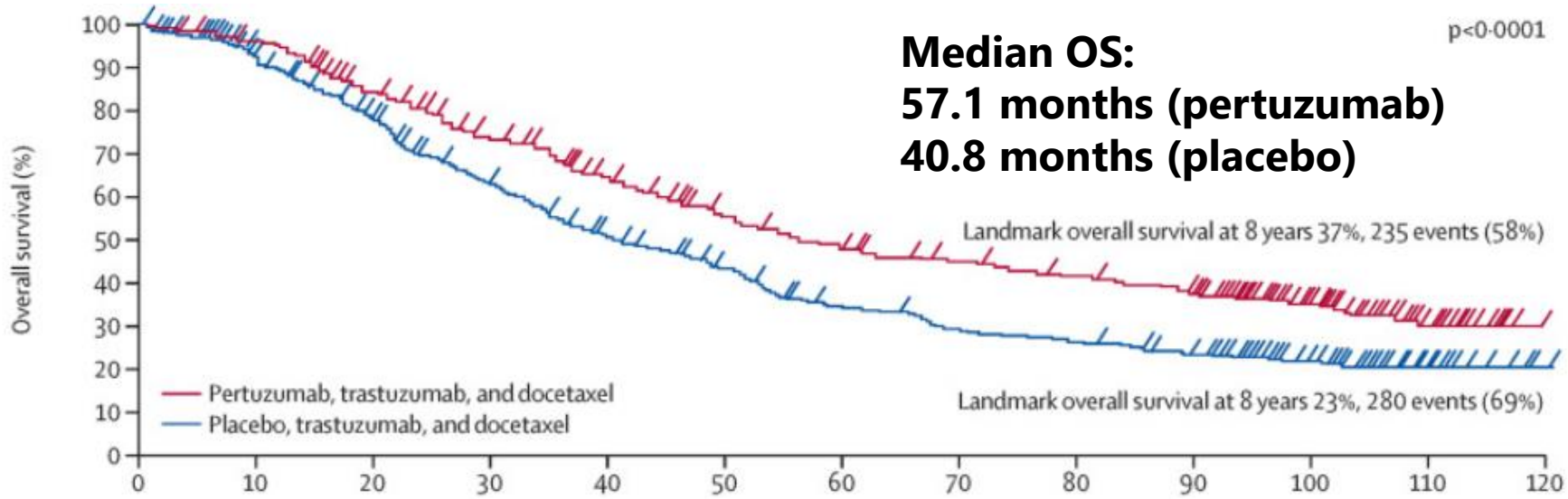
PFS (final)

CLEOPATRA
Median follow up 99.9 months



OS (final)

Median OS:
57.1 months (pertuzumab)
40.8 months (placebo)



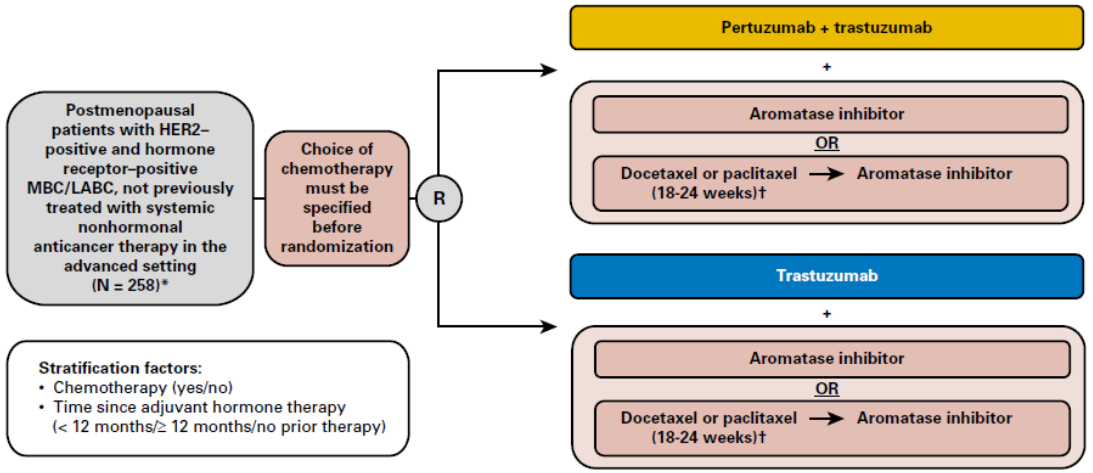
Long-term responders more likely to be:

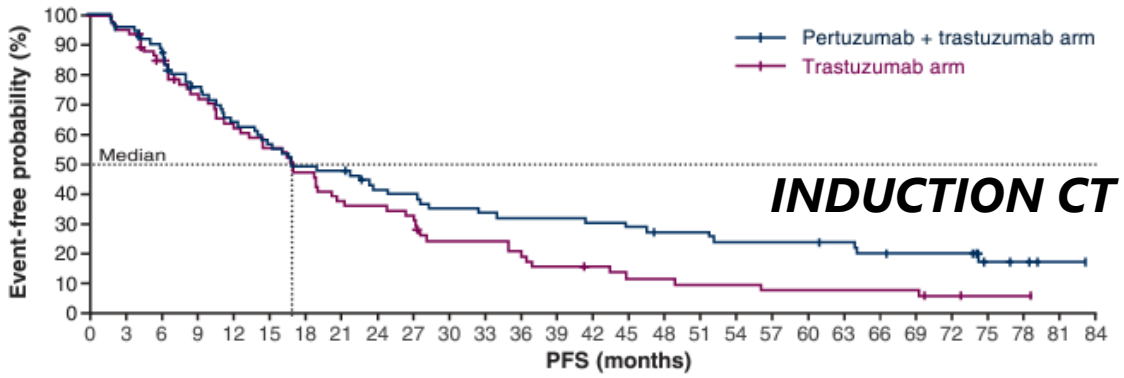
- De-novo presentation
- Non-visceral disease
- Oligometastatic
- PIK3CA WT
- HER2 3+ and higher ERBB2 mRCA
- Higher TILs

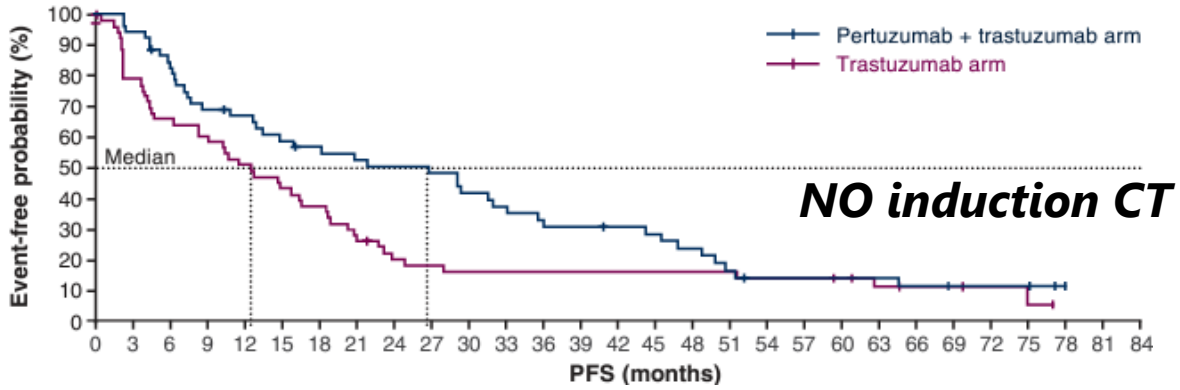
Baselga et al, NEJM 2012; Swain et al Lancet Oncol 2020

CRYSTALLIZED 1st line scenario – what about ET?

PERTAIN







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

CRYSTALLIZED 1st line scenario – what about ET?
Role of CDK 4/6i

- Trials conducted in pre-treated patients reported promising efficacy with anti-HER2 tx + ET+CDK 4/6i: e.g. MonarcHER, PATRICIA

CRYSTALLIZED 1st line scenario – what about ET?
Role of CDK 4/6i

- Trials conducted in pre-treated patients reported promising efficacy with anti-HER2 tx + ET+CDK 4/6i: e.g. MonarcHER, PATRICIA

DETECT-V

*Capecitabine, Docetaxel, Paclitaxel, Vinorelbine, Eribulin, nab-Paclitaxel

**Fulvestrant, Exemestane, Letrozole, Anastrozole, GnRH-analogue

***Ribociclib added to both treatment arms with first amendment

HER2+ MBC
- **HR+/HER2+ primary tumor**
- **1st-3rd line**

N=270

R

Chemotherapy* Trastuzumab/ Pertuzumab

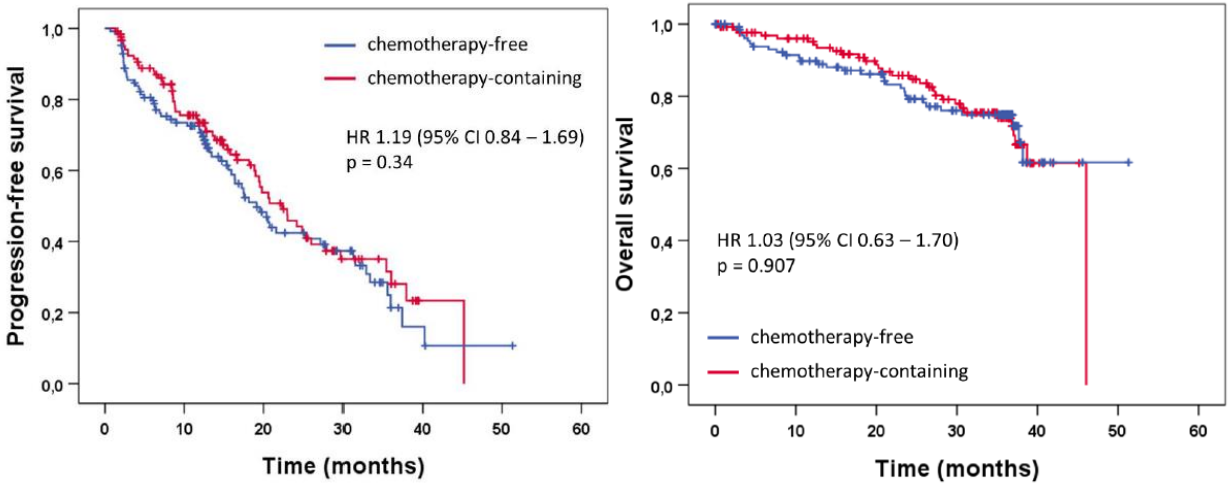
Maintenance therapy Endocrine therapy + Ribociclib*** Trastuzumab/Pertuzumab**

Endocrine therapy + Ribociclib Trastuzumab/ Pertuzumab**

Janni et al, ESMO 2024

- **>75% FIRST-LINE SETTING**
- **>50% visceral involvement**

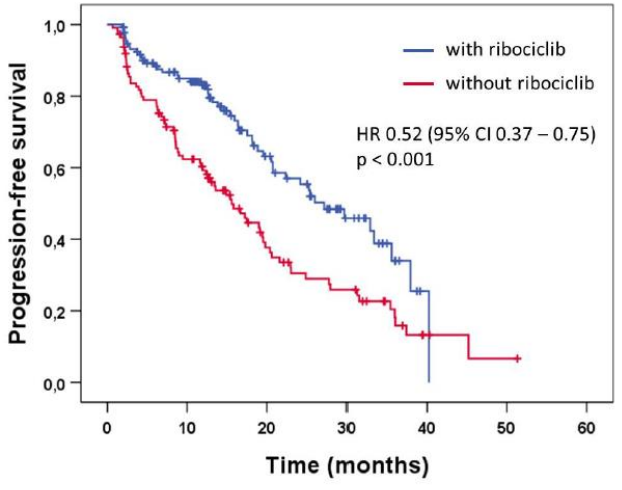
CT-free versus CT-containing



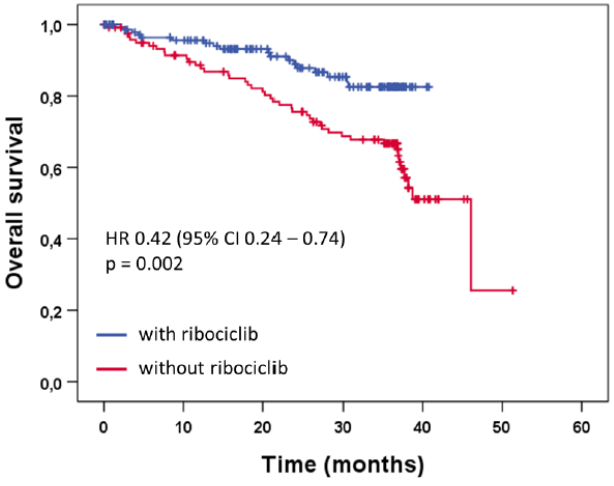
Adjusted multivariable analysis:
HR 1.18 (95% CI 0.81 – 1.72), p = 0.381

Adjusted multivariable analysis:
HR 1.07 (95% CI 0.62 – 1.82), p = 0.816

Ribo versus NO-ribo (no randomization)



Adjusted multivariable analysis:
HR 0.57 (95% CI 0.39 – 0.85), p = 0.005



Adjusted multivariable analysis:
HR 0.47 (95% CI 0.26 – 0.85), p = 0.013

HISTORICAL 2nd line scenario – T-DM1

EMILIA

HER2+ LABC or MBC

- **Prior taxane and trastuzumab**
- **PD on metastatic treatment or within 6 mos of adjuvant treatment**

N=980

R

T-DM1

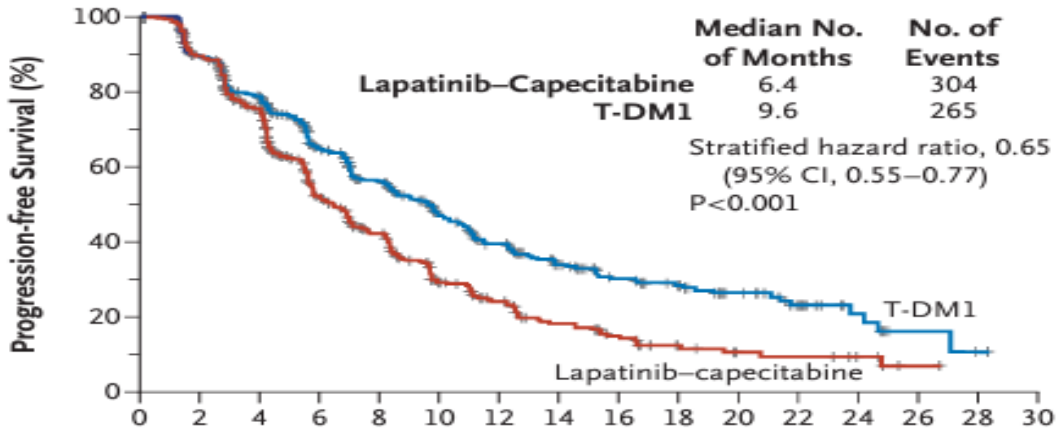
Capecitabine + Lapatinib

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

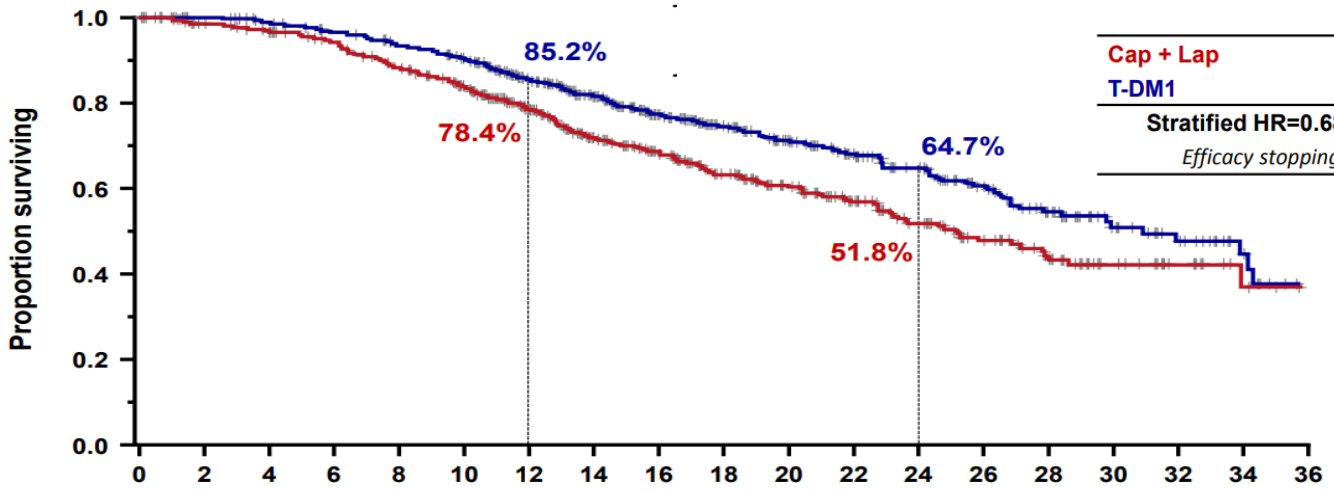
HISTORICAL 2nd line scenario – T-DM1

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 – T-DXd

Destiny-Breast03

HER2+ LABC or MBC

- **Prior taxane and trastuzumab in advanced/metastatic setting**
- **Could have clinically stable, treated BMs**

N=524

R

Trastuzumab Deruxtecan

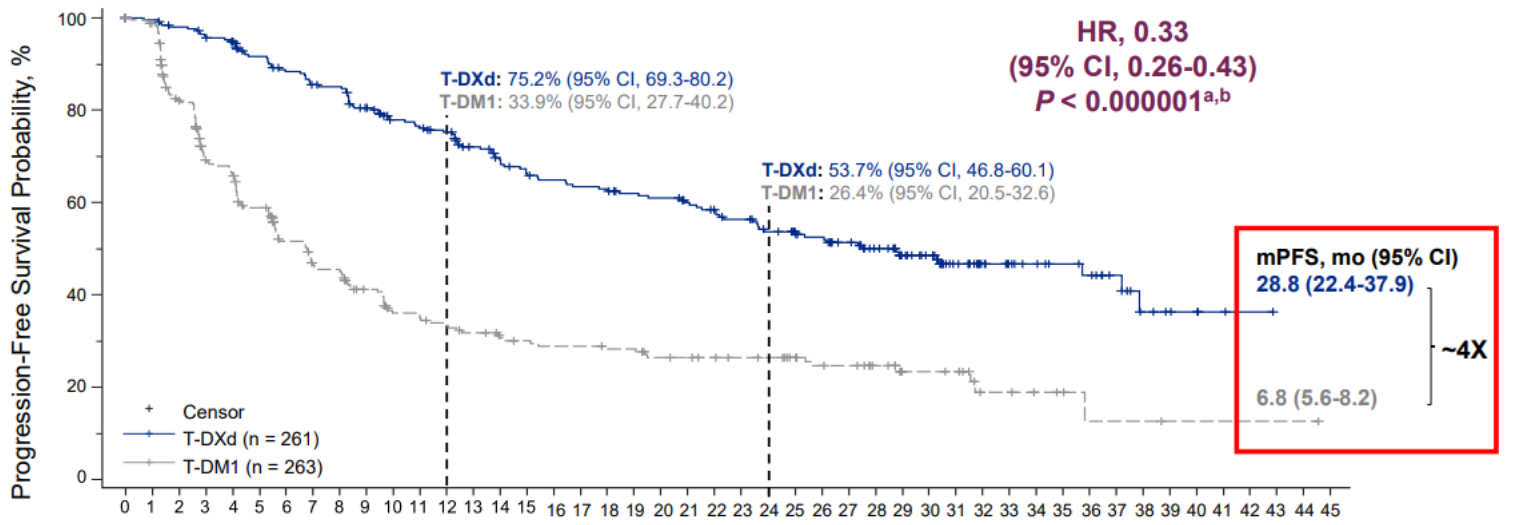
T-DM1

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

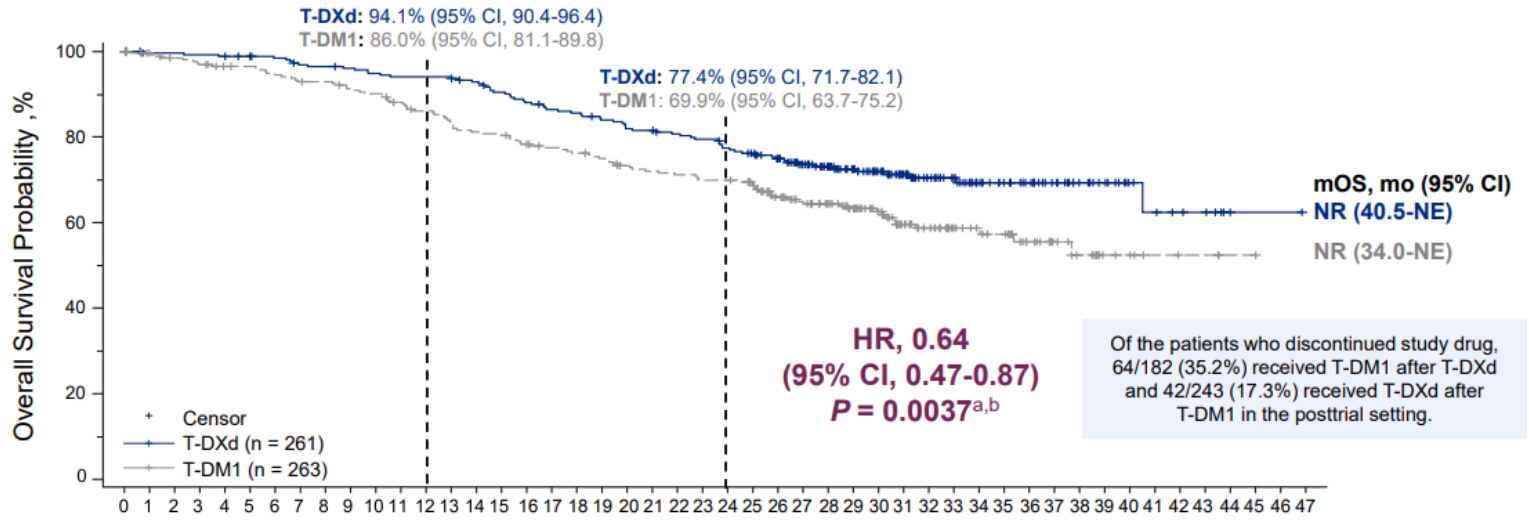
CONTEMPORARY 2nd line scenario – T-DXd

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 2

CONTEMPORARY 3rd line scenario – T-DXd in patients already treated with T-DM1

Destiny-Breast02

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

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

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
  or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

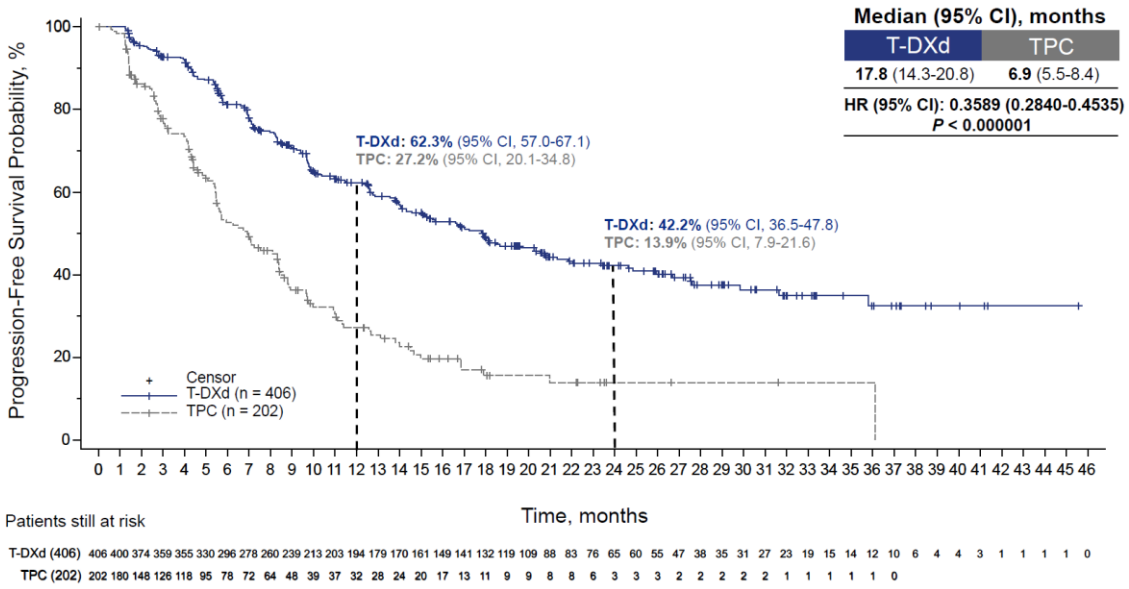
Key secondary endpoint
- OS

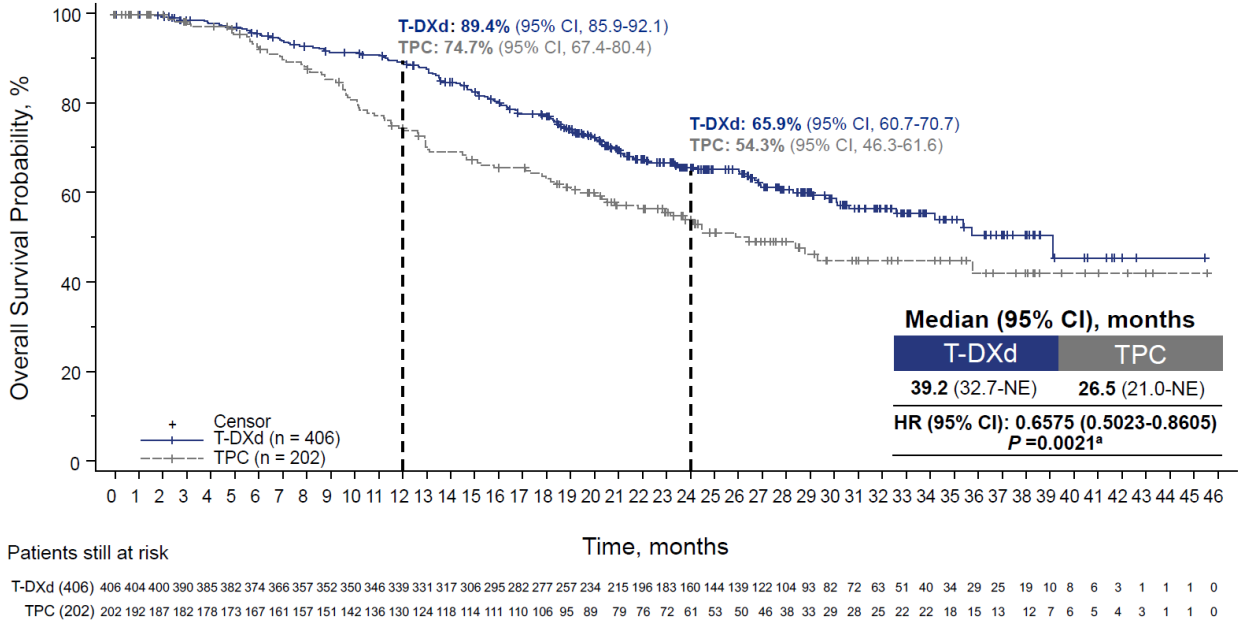
Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm





Krop et al, SABCS 2022; André et al, Lancet Oncol 2023

CONTEMPORARY 3rd line scenario – today: TUCATINIB

HER2CLIMB

HER2+ LABC or MBC

- **Prior trastuzumab, pertuzumab and T-DM1**
- **Brain MRI at baseline**
  - Previously treated BMs
  - Untreated BMs not needing immediate local tx
  - Previously treated progressing BMs not needing immediate local tx
  - No evidence of BMs

N=612

R

Tucatinib + Trastuzumab + Capecitabine

Placebo + Trastuzumab + Capecitabine

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

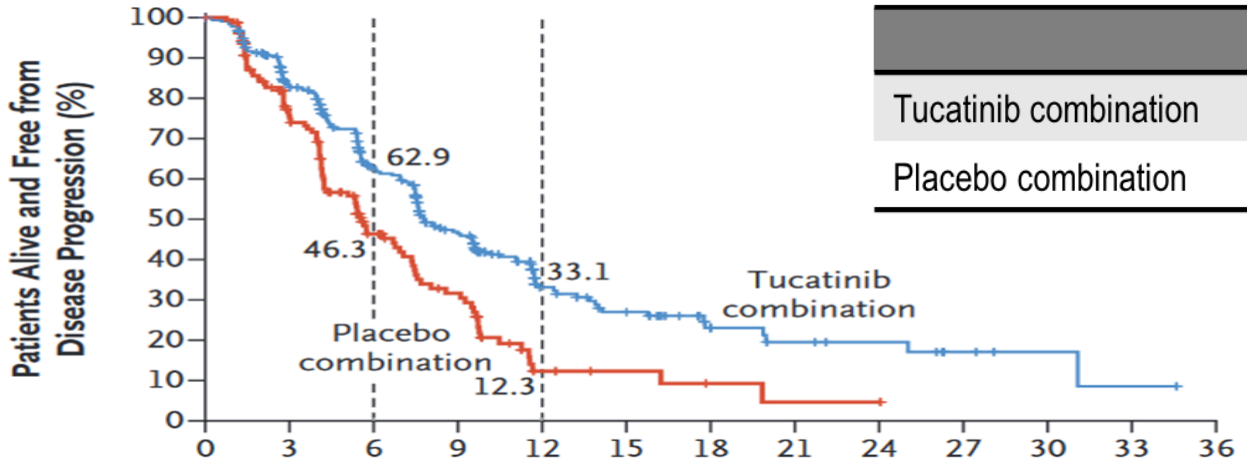
(The size of the trial population was later increased to approximately 600 patients to ensure sufficient power to show a progression-free survival benefit among the patients with brain metastases.)

- **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 – today: TUCATINIB

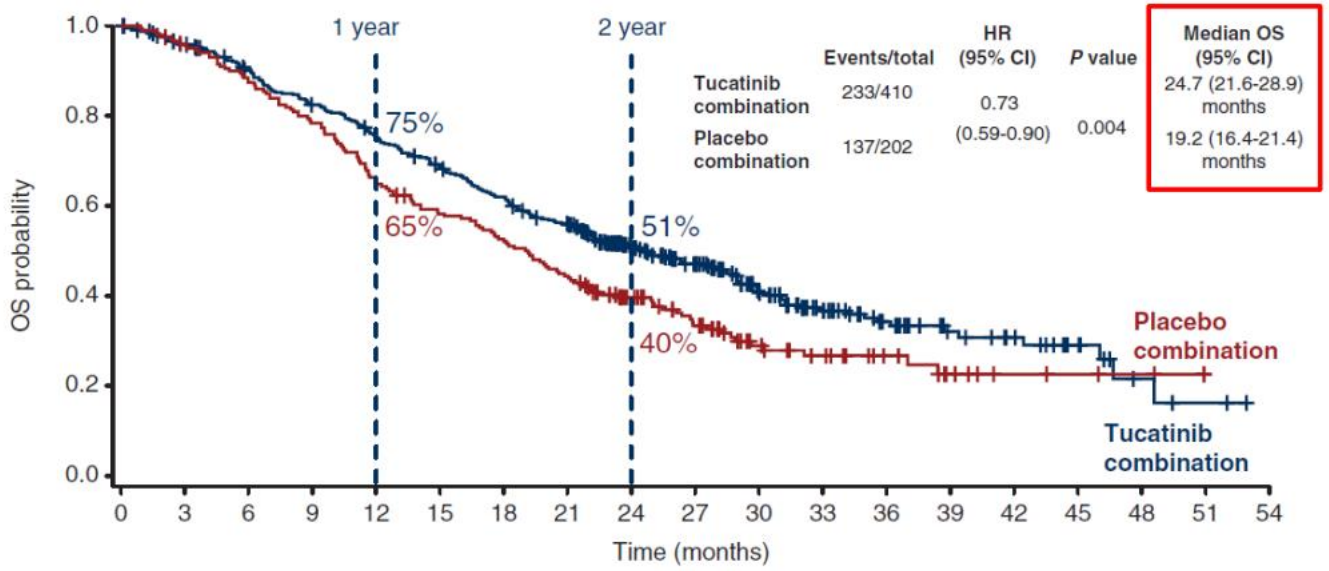
HER2CLIMB

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)

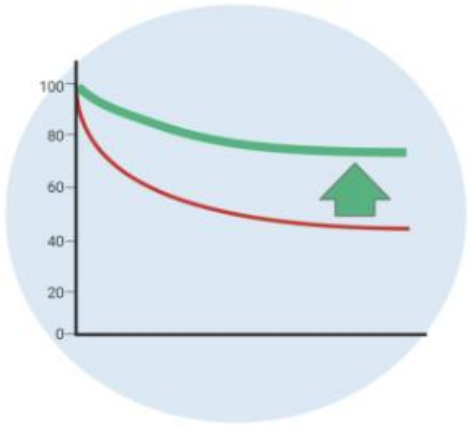
OS (update)



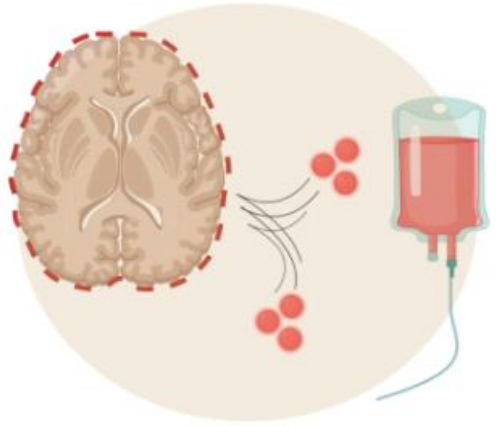
Murthy RK, et al. N Engl J Med 2020; Curigliano et al, Ann Oncol 2022

Brain mets in HER2+ disease

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

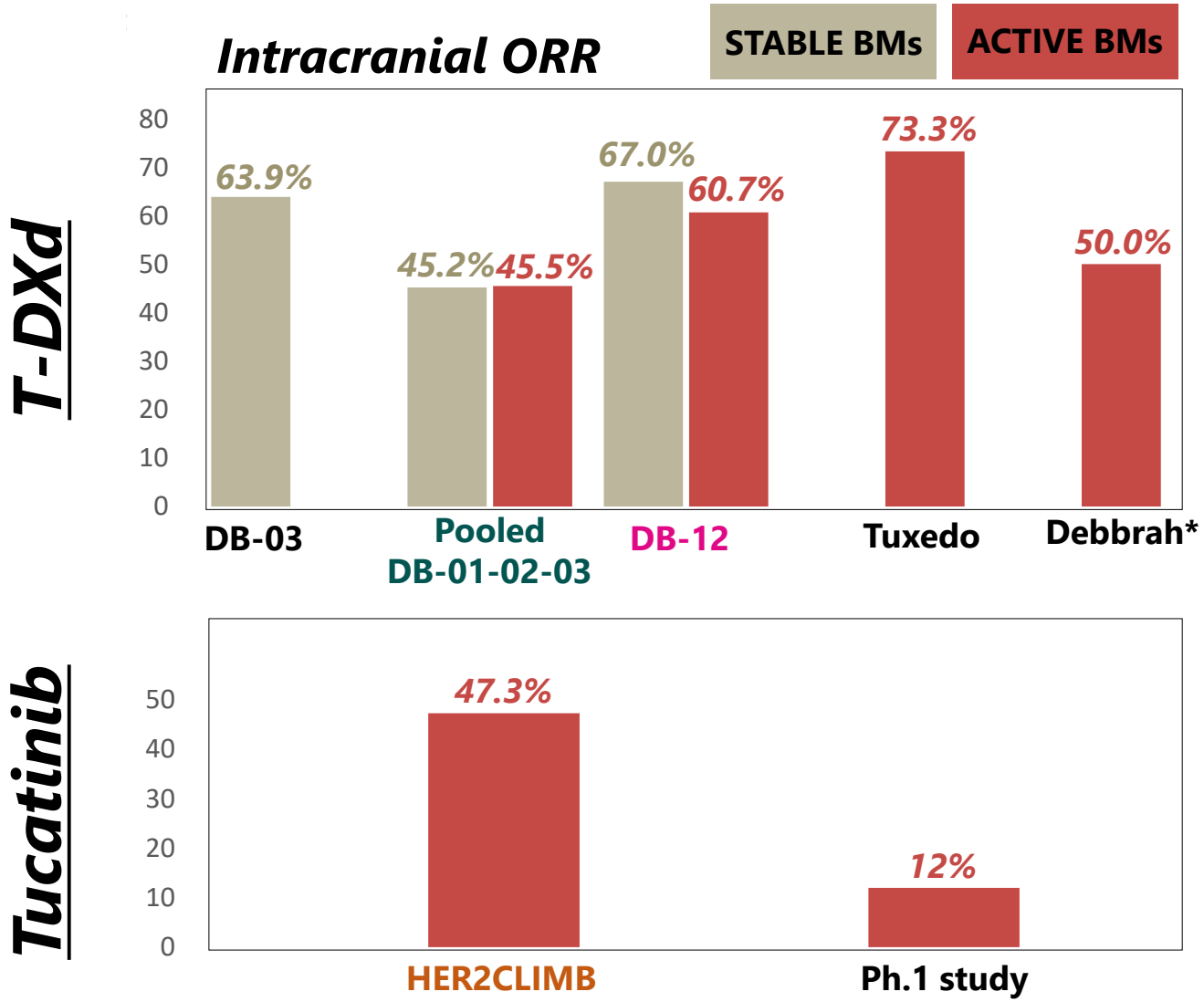


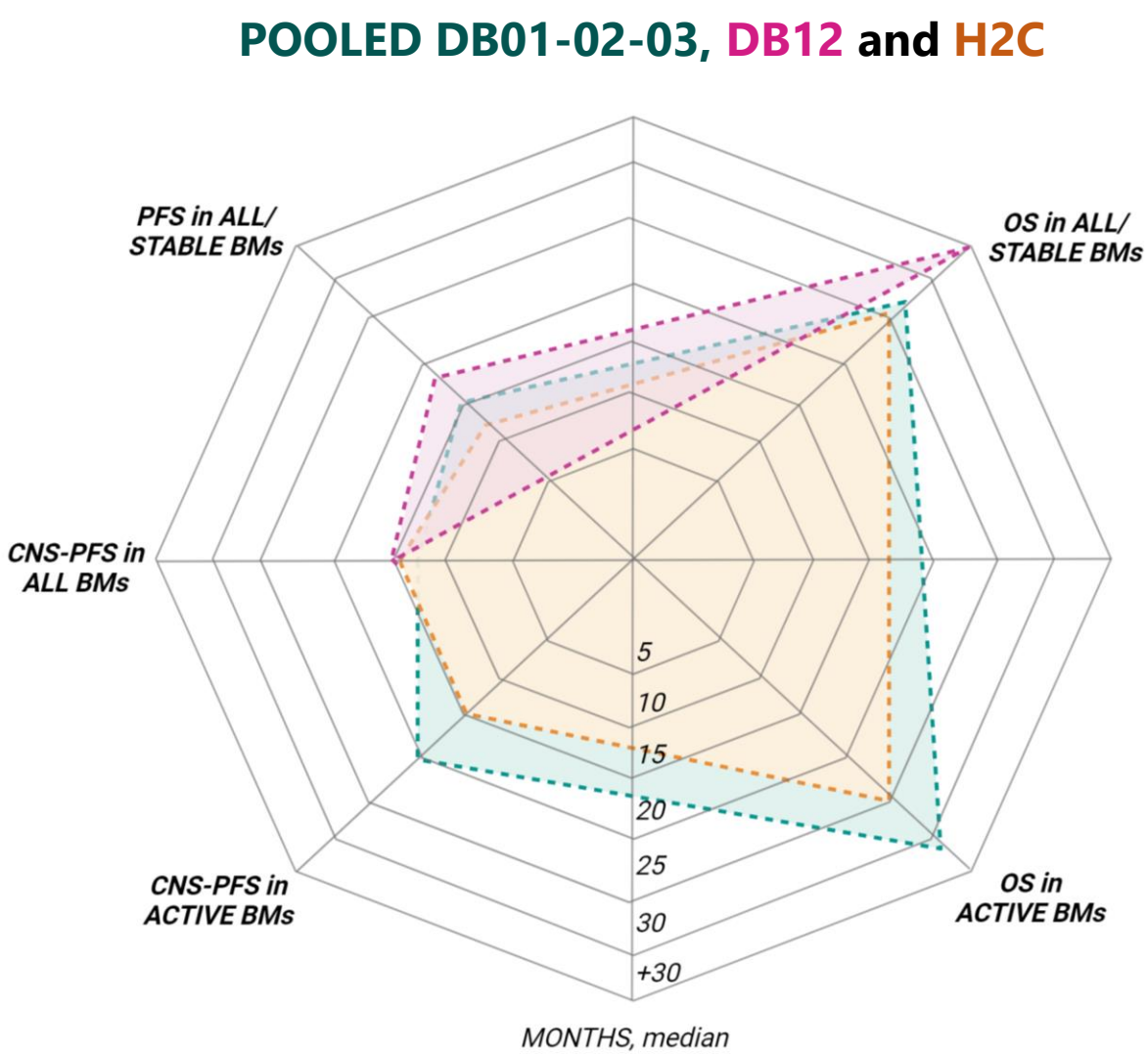
Prolonged survival and better extra-CNS disease control
with contemporary regimens for eBC and mBC



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

Prospective evidence base for T-DXd and Tucatininb benefit in patients with HER2+ mBC and BRAIN mets



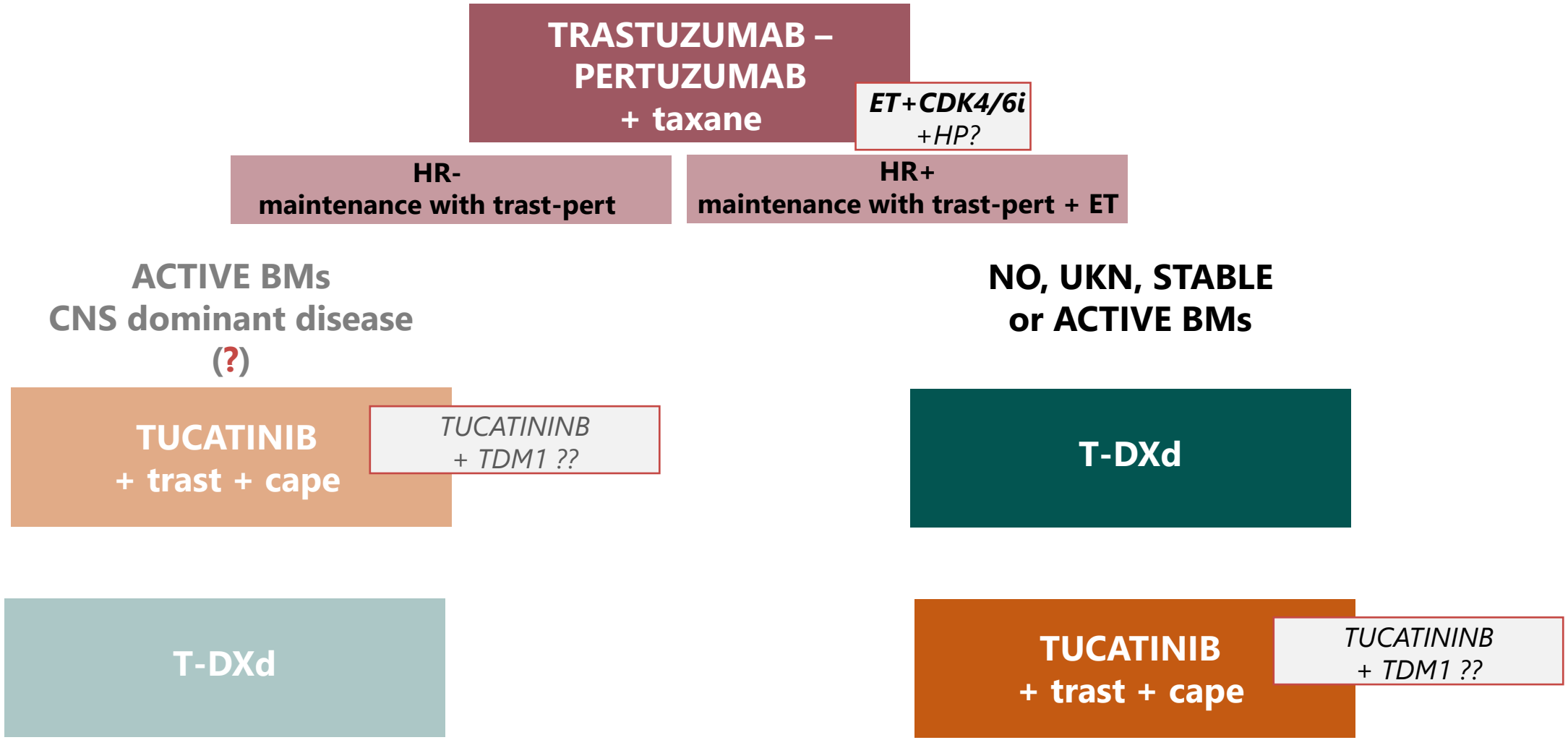


*cohort with untreated BMs (ORR-IC in previously treated and progressing: 44.4%)

Bartsch R, et al. *Nat Med*. 2022. Anders C, et al ESMO Breast Cancer 2024. HurvitzSA, et al. ESMO 2023. Pérez-García JM, et al. *Neuro Oncol*. 2023. Niikura N, et al. *NPJ Breast Cancer*. 2023. Niikura N, et al. *NPJ Breast Cancer*. 2023. Lin et al, ESMO 2024. Filho et al, Ann Oncol 2020

Radar chart: Intellectual property F Miglietta

Treatment algorithm (focus on systemic tx)



Gennari et al, Ann Oncol 2021; ESMO living guidelines

Treatment algorithm (focus on systemic tx)

TRIAL
IN PROGRESS

TBCRC-SAPPHO
THP → T-DXd → TDM1/tucatininb → HP/tucatininb → STOP

HEROES
Discont. anti-HER2

STOP-HER/TBCRC062
Discont. anti-HER2

DB09
T-DXd (+/- pert)

TRASTUZUMAB – PERTUZUMAB + taxane

DETECT-V
Ribo+ET*+trast-pert*

ET+CDK4/6i *+HP?*

HR-
maintenance with trast-pert

HR+
maintenance with trast-pert + ET

heredERA
Giredestrant*+trast-pert*

PATINA
Palbo*+AI +trast-pert*

HER2CLIMB05
Tucatinib*+trast-pert*

ACTIVE BMs
CNS dominant disease
(?)

TUCATINIB
+ trast + cape

T-DXd

NO, UKN, STABLE
or ACTIVE BMs

T-DXd

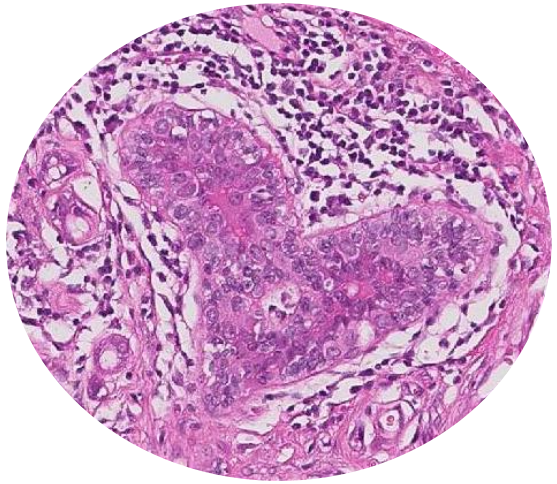
TUCATINIB
+ trast + cape

Empowher-BC-303
Zanidatamab *+CT*

Adapted from Gennari et al, Ann Oncol 2021; ESMO living guidelines

Grazie

Federica Miglietta



federica.miglietta@unipd.it

@FedeMiglietta