ESMO DEEP DIVE:
BREAST CANCER

HER2+ METASTATIC BREAST CANCER: REFINING PRACTICE AND STEERING RESEARCH

Peter Schmid, *Chair*

Barts Cancer Institute
London

ESMO WEBINAR SERIES

PROGRAMME AND SPEAKERS

4 September 2024

5 min	**Welcome and introduction** Peter Schmid
15 min	**Brain metastases: Prevention, screening and management** Nancy Lin
15 min	**Optimal treatment sequences after guideline-based early breast cancer therapy** Volkmar Müller
15 min	**Do we need to think about other targets as well?** Giuseppe Curigliano
15 min	**What's the role of the molecular tumour board-emerging concepts** Barbara Pistilli
15 min	**QnA and Discussion** All speakers

Peter Schmid
Chair
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Nancy U. Lin
Speaker
Associate Chief, Division of Breast Oncology, Dana-Farber Cancer Institute (DFCI), Boston, MA

Volkmar Müller
Speaker
Department of Gynecology and University Breast Center, University Medical Center Hamburg-Eppendorf (UKE)

Giuseppe Curigliano
Speaker
University of Milan and European Institute of Oncology, IRCCS
Milan

Barbara Pistilli
Speaker
Gustave Roussy, Villejuif

LEARNING OBJECTIVES

- To acquire a deeper understanding of the clinical course of breast cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for breast cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

ESMO DEEP DIVE:
BREAST CANCER

THANK YOU FOR YOUR ATTENTION

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ESMO WEBINAR SERIES

ESMO DEEP DIVE:
BREAST CANCER

BRAIN METASTASES:

Prevention, Screening, and Management

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SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

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ESMO DEEP DIVE:
BREAST CANCER

DECLARATION OF INTERESTS

Institutional research support: Genentech/Roche, Pfizer, Merck, Seattle Genetics, Zion Pharmaceuticals, Olema Pharmaceuticals, AstraZeneca

Consulting Honoraria: Seattle Genetics, Daichii-Sankyo, AstraZeneca, Olema Pharmaceuticals, Janssen, Blueprint Medicines, Stemline/Menarini, Eisai

Royalties: Up to Date

Travel: Olema Pharmaceuticals

KEY REFERENCES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

E. Le Rhun[1,2], M. Guckenberger[3], M. Smits[4], R. Dummer[5], T. Bachelot[6], F. Sahm[7], N. Galldiks[8,9,10], E. de Azambuja[11], A. S. Berghoff[12], P. Metellus[13,14], S. Peters[15], Y.-K. Hong[16], F. Winkler[17], D. Schadendorf[18,19], M. van den Bent[20], J. Seoane[21,22], R. Stahel[23], G. Minniti[24,25], P. Wesseling[26,27], M. Weller[2] & M. Preusser[12], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

International Consensus Guidelines for Advanced Breast Cancer
ABC GUIDELINES

ABC1 ABC2 ABC3 ABC4 ABC5 ABC6 ABC7

ASCO special articles

Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Guideline Update

Naren Ramakrishna, MD, PhD[1]; Carey K. Anders, MD[2]; Nancy U. Lin, MD[3]; Aki Morikawa, MD, PhD[4]; Sarah Temin, MSPH[5]; Sarat Chandarlapaty, MD, PhD[6]; Jennie R. Crews, MD[7]; Nancy E. Davidson, MD[8]; Maria Alice B. Franzoi, MD[9]; Jeffrey J. Kirshner, MD[10]; Ian E. Krop, MD, PhD[3]; Debra A. Patt, MD, MPH, MBA[11]; Jane Perlmutter, PhD[12]; and Sharon H. Giordano, MD, MPH[13]

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024 Brain Metastases

LeRhun et al, Ann Oncol 2021; Ramakrishna et al, JCO 2022; Cardoso et al, Breast 2024; www.nccn.org/guidelines

INCIDENCE OF BRAIN METASTASES IN PTS WITH HER2+ MBC

RWD from U.S. Flatiron Database

Line of therapy	HR+, HER2-positive	HR–, HER2-positive	HR+, HER2– [HR+, HER2-low]	TNBC [HR–, HER2-low]
Number of pts, n				
1	3062	902	12331 [7062]	1780 [725]
2	1936	478	8120 [4721]	972 [422]
3	1232	281	5303 [3101]	526 [240]
4	761	159	3454 [2002]	283 [129]
5+	453	103	2191 [1276]	141 [70]
Prevalence of BM, %				
1	193 (6.3)	101 (11.2)	134 (2.5) [199 (2.8)]	109 (10.3) [88 (12.1)]
2	341 (17.6)	149 (31.2)	150 (4.4) [275 (5.8)]	97 (17.6) [73 (17.3)]
3	265 (21.5)	102 (36.3)	125 (6.7) [231 (7.4)]	63 (22.0) [50 (20.8)]
4	199 (26.1)	59 (37.1)	104 (7.2) [189 (9.4)]	38 (24.7) [36 (27.9)]
5+	120 (26.5)	38 (36.9)	78 (8.5) [134 (10.5)]	23 (32.4) [18 (25.7)]

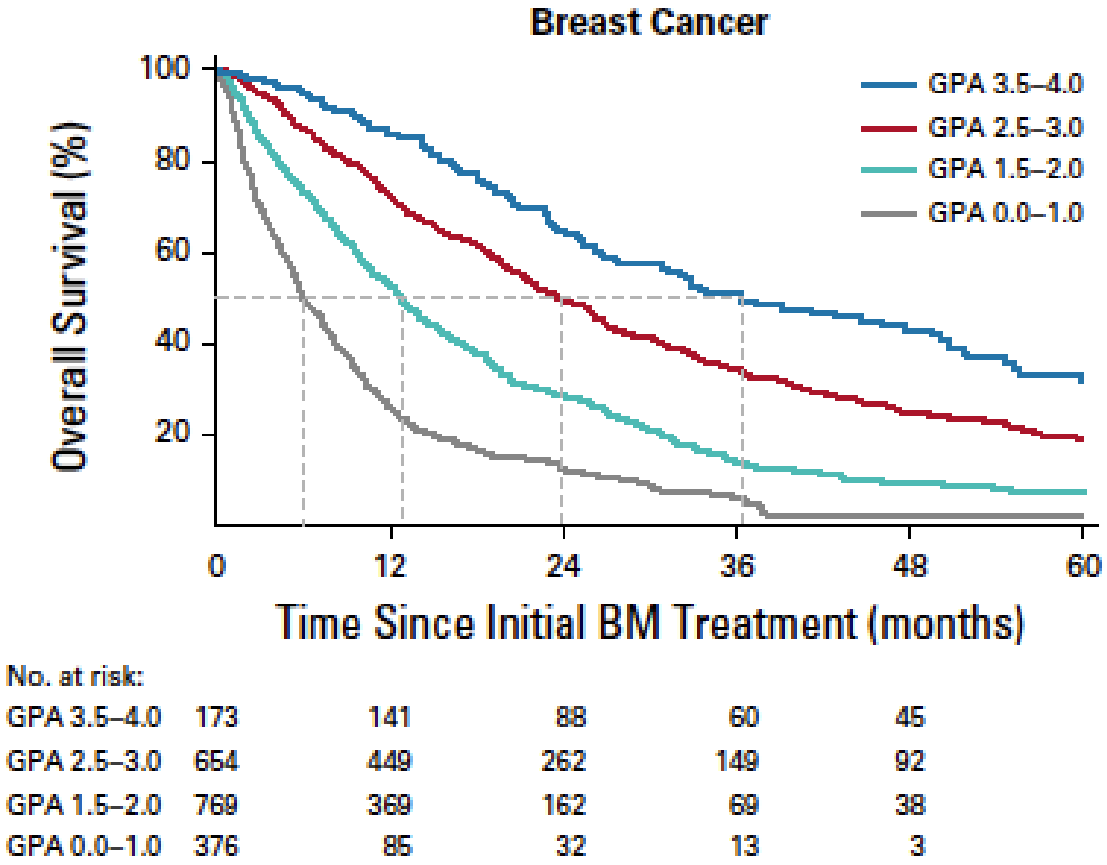
Sammons et al, SABCS 2023

Data from 18,075 patients with MBC in the Flatiron database who had initiated a 1L of therapy up to March 1, 2021 to allow at least 2y follow-up

By 3L of therapy, **21.5%** of HR+/HER2+ and **36.3%** of HR-/HER2+ pts have developed brain metastases

Older data from the HERA trial (Pestalozzi et al, Lancet Oncol 2013) where HER2+ pts were followed until death reported that **47%** of trastuzumab-treated pts eventually developed brain mets

SURVIVAL AFTER BM DIAGNOSIS IS MOST FAVORABLE IN PATIENTS WITH HER2+ MBC



Prognostic Factor by Cancer Type	GPA 0	0.5	1.0	1.5	2.0	Patient Score
Breast cancer						
KPS	≤ 60	70-80	90-100	NA	NA	
Age, years	≥ 60	< 60	NA	NA	NA	
No. of BM	≥ 2	1	NA	NA	NA	
ECM	Present	Absent	NA	NA	NA	
Subtype	Basal	Luminal A	NA	Her2 or Luminal B	NA	
					Sum =	MS (months) by GPA: 0-1 = 6; 1.5-2.0 = 13; 2.5-3.0 = 24; 3.5-4.0 = 36

Sperduto et al, JCO 2020

SHOULD WE SCREEN ASYMPTOMATIC PATIENTS WITH HER2+ MBC FOR BRAIN METASTASES?

SHOULD WE SCREEN ASYMPTOMATIC HER2+ MBC PATIENTS FOR BRAIN METASTASES?

”Brain imaging should not be routinely performed in asymptomatic patients. This approach is applicable to all patients with ABC including those with HER2+ and/or triple-negative ABC.”

”There are insufficient data to recommend for or against performing routine magnetic resonance imaging to screen for brain metastases; clinicians should have a low threshold for MRI of the brain because of the high incidence of brain metastases among patients with HER2+ advanced breast cancer.”

“Screening at diagnosis is potentially justified in HER2+ and TN MBC (EANO: IV, n/a; ESMO IV, B). This approach will result in a higher rate of detection of asymptomatic BM.”

Cardoso et al, Breast 2024; Ramakrishna et al, JCO 2022; LeRhun et al, Ann Oncol 2021

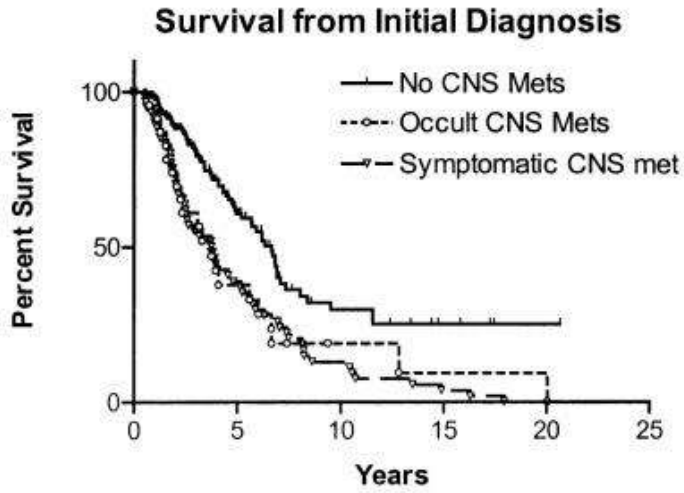
DOES IDENTIFICATION OF OCCULT BM IMPACT OS?

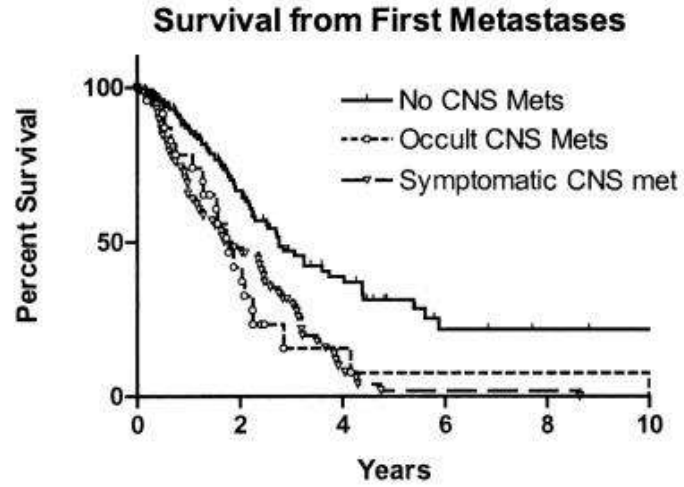
Retrospective analysis of pts screened as part of clinical trials

Nearly all pts with occult BM received WBRT

No difference in OS between pts with occult vs symptomatic BM

21 of 23 pts with occult BM and known end-of-life details: all died of systemic disease progression without CNS symptoms





Miller et al, Ann Oncol 2003

A NATURAL EXPERIMENT: OUTCOMES OF BM PTS WITH NSCLC (SCREENED) VS BREAST CA (NOT SCREENED)

Parameter	Patients With Breast Cancer (N = 349)	Patients With NSCLC (N = 659)	*P* Value
Brain-Related Characteristics at Diagnosis of BM			
Largest BM diameter, mm			
Mean (SD)	20 (13)	17 (11)	<.001[i]
Median (IQR)	17 (10-29)	14 (8-23)	
With BM, >3 cm, No. (%)[c]	62 (18.5)	81 (12)	.01[k]
No. of BM			
Mean (SD)	11 (28)	5 (12)	<.001[i]
Median (IQR)	3 (1-8)	2 (1-4)	
With >4 BM, No. (%)[d]	131 (38.5)	137 (20.9)	<.001[k]
Neurological symptoms, No. (%)[e]	265 (75.9)	399 (60.5)	<.001[k]
Seizures, No. (%)[f]	59 (16.9)	75 (11.4)	.01[k]
Leptomeningeal disease, No. (%)[g]	40 (11.5)	14 (2.1)	<.001[k]
Brainstem involvement, No. (%)	28 (8.0)	28 (4.2)	.02[k]
Initial Treatment for BM			
Systemic therapy only[h]	56 (16.0)	79 (12.0)	<.001[m]
Craniotomy plus stereotactic radiation therapy	29 (8.3)	83 (12.6)	
Craniotomy plus WBRT	20 (5.7)	58 (8.8)	
Stereotactic radiation only	55 (15.8)	213 (32.3)	
WBRT only	163 (46.7)	201 (30.5)	
WBRT plus stereotactic radiation therapy	22 (6.3)	18 (2.7)	
Craniotomy plus WBRT plus stereotactic radiation therapy	4 (1.1)	7 (1.1)	
Outcomes After Initial Treatment for BM			
Survival, median (95% CI), y	1.45 (1.29-1.65)	1.09 (0.98-1.20)	.06[n]
Neurological death, No. (%)[j]	103 (37.3)	98 (19.9)	<.001[k]

Breast ca pts presented with:
-Larger BM diameter
-More BM
-More frequent neuro symptoms

and experienced:
-more frequent WBRT
-more frequent neurological death

Cagney et al, JAMA Oncol 2018

MULTIPLE PROSPECTIVE BRAIN MRI SCREENING TRIALS ARE UNDERWAY

PI	Inclusion	NCT
Ayal Aizer	MBC, all subtypes IBC treated w/curative intent	NCT04030507
Kamran Ahmed	MBC, all subtypes	NCT05115474
Katarzyna Jerzak	HER2+ or TNBC MBC	NA
Seung-koo Lee	HER+ or TNBC MBC	NA (Kim et al, SABCS 2023)

HOW SHOULD WE MANAGE PATIENTS WITH BRAIN METASTASES FROM HER2+ BREAST CANCER?

INITIAL MANAGEMENT OF NEW BRAIN METASTASES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Recommendations

- The multimodality treatment of BMs should be based on a careful individualised estimation of the different contributions from surgery, radiation oncology and medical oncology [EANO: IV, n/a; ESMO: V, B].
- Ideally, therapeutic decisions should be discussed at a dedicated BM board or at a disease-specific tumour board with participation of colleagues experienced in the management of CNS tumours [EANO: IV, n/a; ESMO: V, B].

Patients with a single or a small number of potentially resectable BM should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable BM

Because patients with HER2+ ABC and BM can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. SRS) should be preferred to WBRT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).

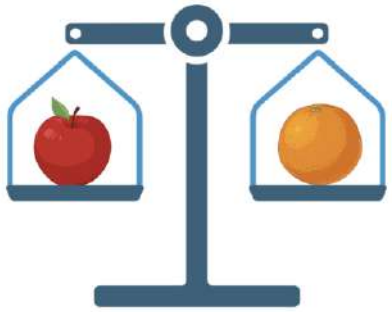
In patients with HER2+ ABC who develop brain metastases with stable extracranial disease, for whom SRS is feasible and acceptable, systemic therapy should not be changed.

LeRhun et al, Ann Oncol 2021; Cardoso et al, Breast 2024

WEIGHING LOCAL THERAPY VS SYSTEMIC THERAPY

Favors Local Therapy

Controlled extracranial disease
Desire to maintain systemic regimen
More symptomatic lesions
Low brain met velocity
Disease amenable to SRS
Less confidence in systemic tx



Favors Systemic Therapy

Progressive extracranial disease
Need to switch systemic regimen
Less symptomatic lesions
High brain met velocity
Concern for RT toxicity
More confidence in systemic tx

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Brain Metastases

- Tumor Agnostic[b]
  - *NTRK* gene fusion tumors
    - Preferred Regimens
      - Larotrectinib[1]
      - Entrectinib[2]
      - Repotrectinib[3]
    - Other Recommended Regimen
      - TMZ 5/28 Schedule
  - MSI-H/dMMR or TMB-H tumors for isolated brain metastases
    - Preferred Regimen
      - Pembrolizumab (category 2B)[4,5]
- Breast Cancer[c]
  - HER2 positive
    - Preferred Regimens
      - Tucatinib + trastuzumab[d] + capecitabine (category 1) (if previously treated with 1 or more anti-HER2–based regimens)[6]
    - Other Recommended Regimens
      - Fam-trastuzumab deruxtecan-nxki[7,8]
      - Ado-trastuzumab emtansine (T-DM1)[9]
      - Capecitabine + lapatinib[10,11]
      - Capecitabine + neratinib[12,13]
      - Pertuzumab and high-dose trastuzumab[d,14]
      - Paclitaxel + neratinib (category 2B)[15]
  - HER2 non-specific
    - Other Recommended Regimens
      - Capecitabine[16-20]
      - Cisplatin (category 2B)[21,22]
      - Etoposide (category 2B)[21,22]
      - Cisplatin + etoposide (category 2B)[22,23]
      - High-dose methotrexate (category 2B)[e,24]

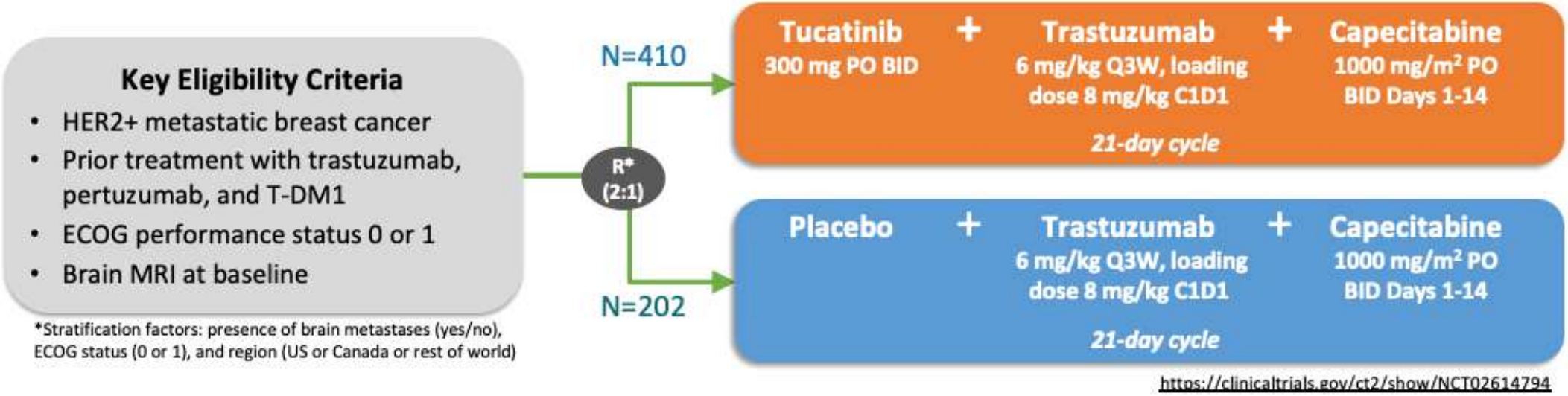
An expanding list of systemic options for patients with HER2+ BM

Also possible to combine trastuzumab with other cytotoxics, e.g. platinums

Cardoso et al, Breast 2024

HER2CLIMB

Benefit of tucatinib in ITT population and in patients with BM



Patients with or without brain mets
PFS HR 0.54; medians 5.6 vs 7.8 months; p <0.001
OS HR 0.66; medians 17.4 months vs 21.9 months; p=0.005

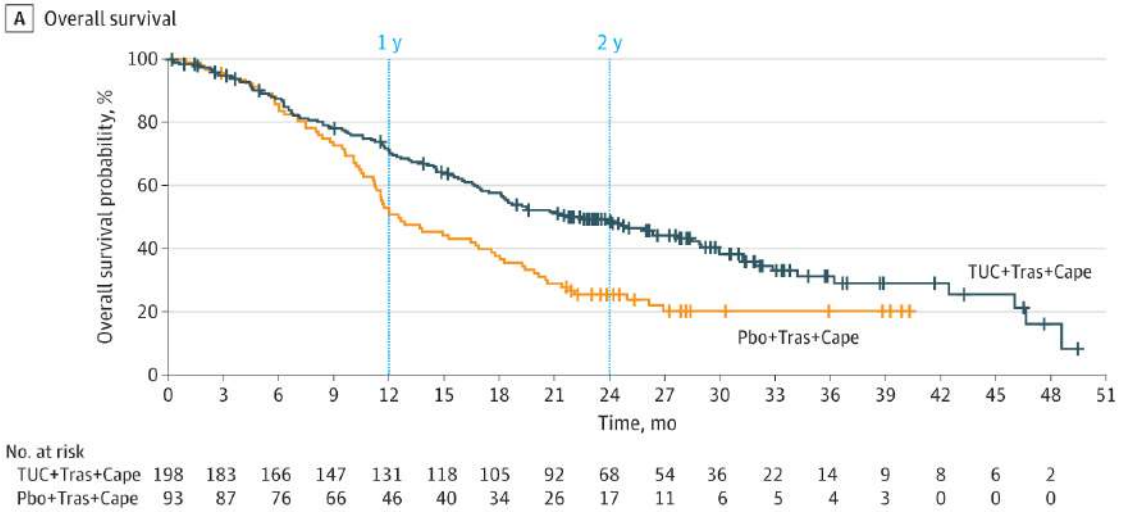
Patients with brain mets
PFS HR 0.48; medians 5.4 vs 7.6 months; p <0.001

Murthy et al, NEJM 2019

HERCLIMB

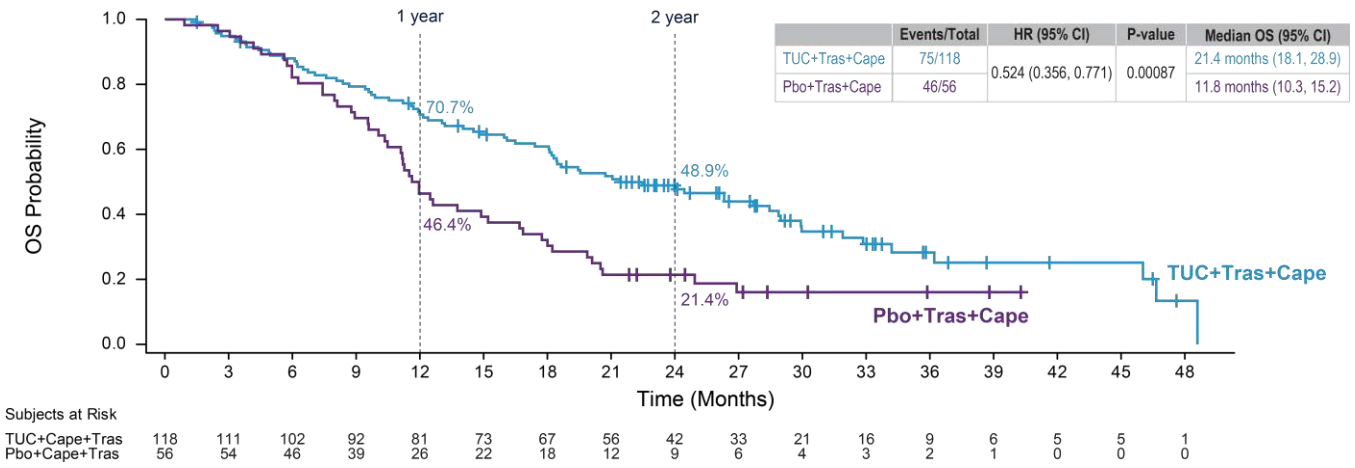
OS benefit in pts with BM, including in pts with active BM

All pts with BM



Median OS 12.5 mo → 21.6 mo
HR 0.6 (0.44, 0.81); p<0.001

Pts with Active BM



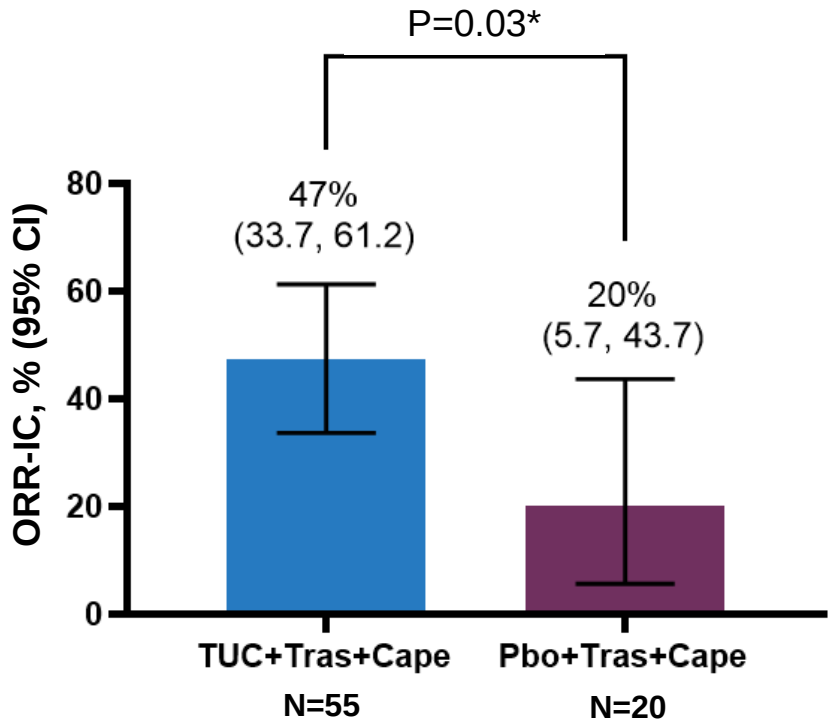
Median OS 11.8 mo → 21.4 mo
HR 0.5 (036, 0.77); p<0.001

Lin et al, JAMA Oncol 2023

HER2CLIMB

Durable intracranial responses in pts with active, measurable BM

Confirmed CNS Objective Response Rate (RECIST 1.1)

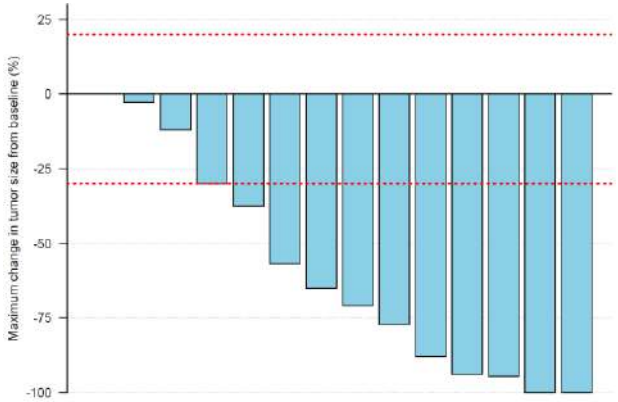


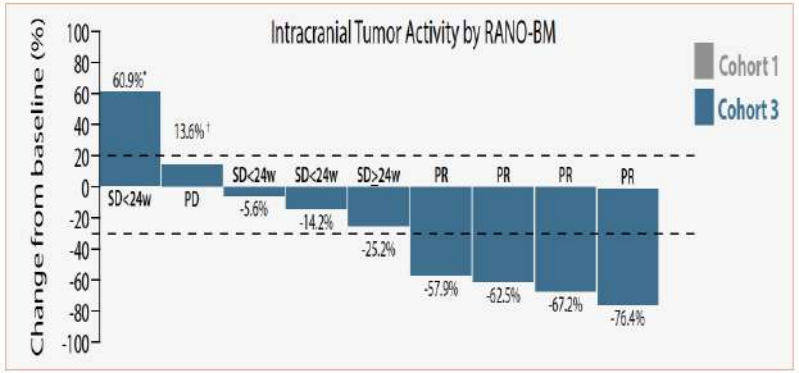
Lin et al, JCO 2020

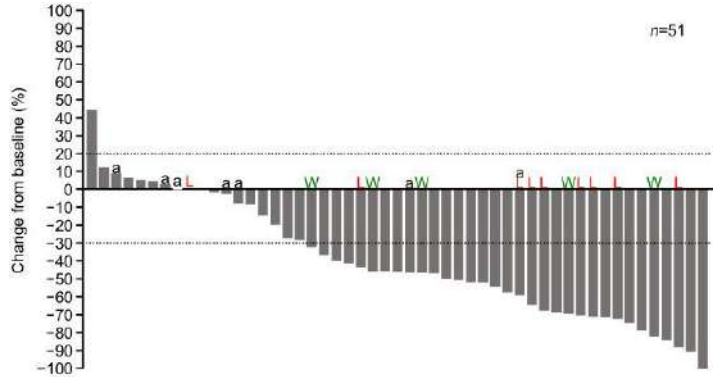
	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

CNS ACTIVITY OF TDXD IN PATIENTS WITH BREAST CANCER







TUXEDO-1 trial
Bartsch et al, Nat Med 2022

ORR-IC = 73% in pts with Active BM

DEBBRAH trial
Vaz Batista et al, Neuro Oncol 2023

ORR-IC = 44% in pts with Active BM

ROSET-BM
Niikura et al, npj Breast 2023

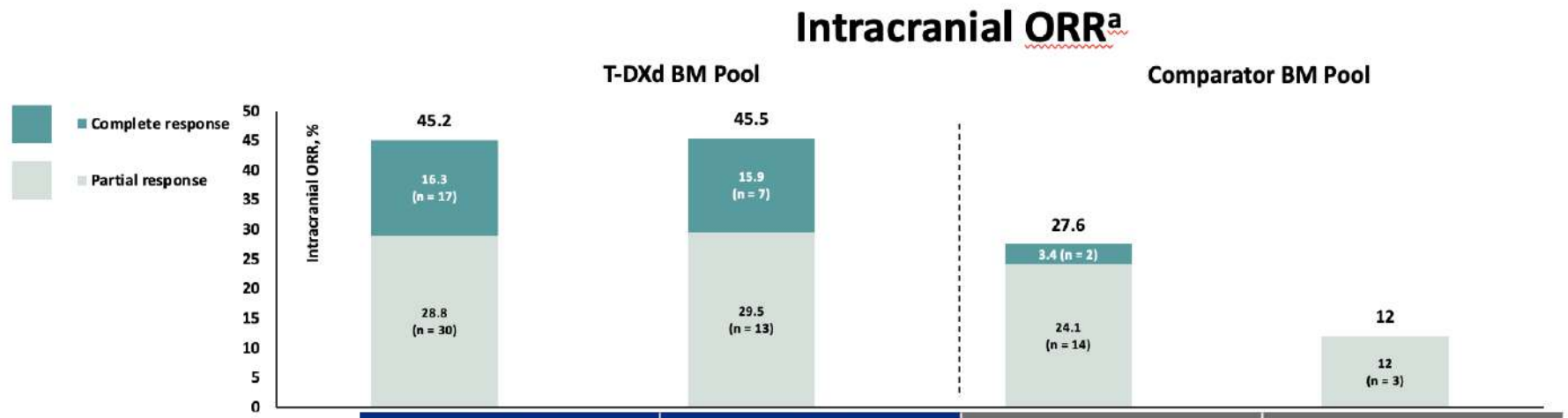
ORR-IC = 62.7%

Bartsch et al, Nat Med 2022; Vaz-Batista et al, Neuro Oncol 2023; Niikura et al, npj Breast 2023

INTRACRANIAL ACTIVITY OF T-DXD

Pooled analysis of DESTINY BREAST-01, -02, and -03

Exploratory Best IC Response, ORR, and DoR per BICR



	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA[b]

T-DXd consistently demonstrated superior rates of IC responses over comparator in patients with treated/stable and untreated/active BMs

A trend in prolonged median IC-DoR was most pronounced in the untreated/active BMs subgroup

Hurvitz et al, ESMO 2023

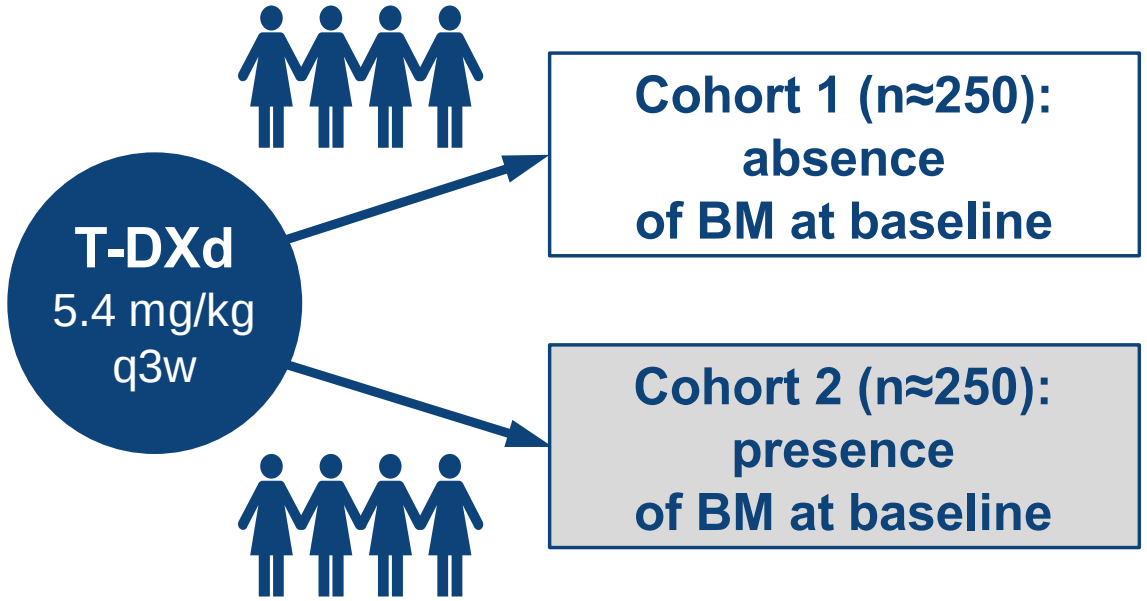
DESTINY-BREAST12

Accrual completed; awaiting results

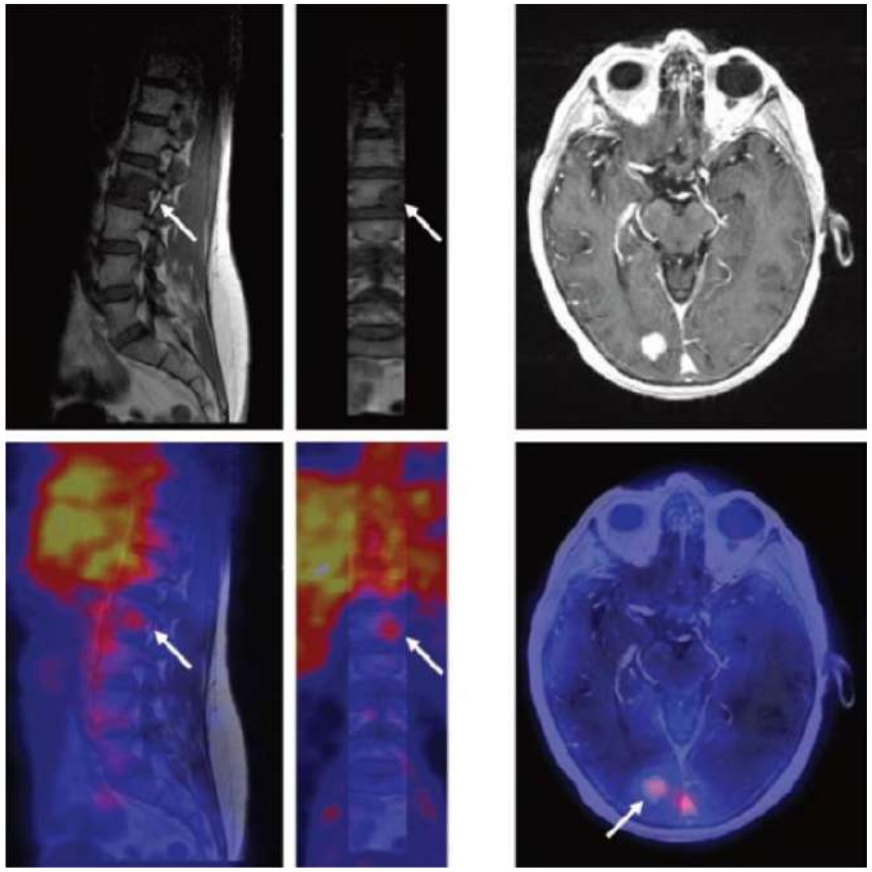
Study Design and Population

Patient population (N≈500)

- HER2-positive advanced or metastatic breast cancer
- Absence or presence of BM at baseline
- ≤2 prior lines of therapy in the metastatic setting



TRASTUZUMAB CROSSES THE DISRUPTED BLOOD-TUMOR-BARRIER (BTB)

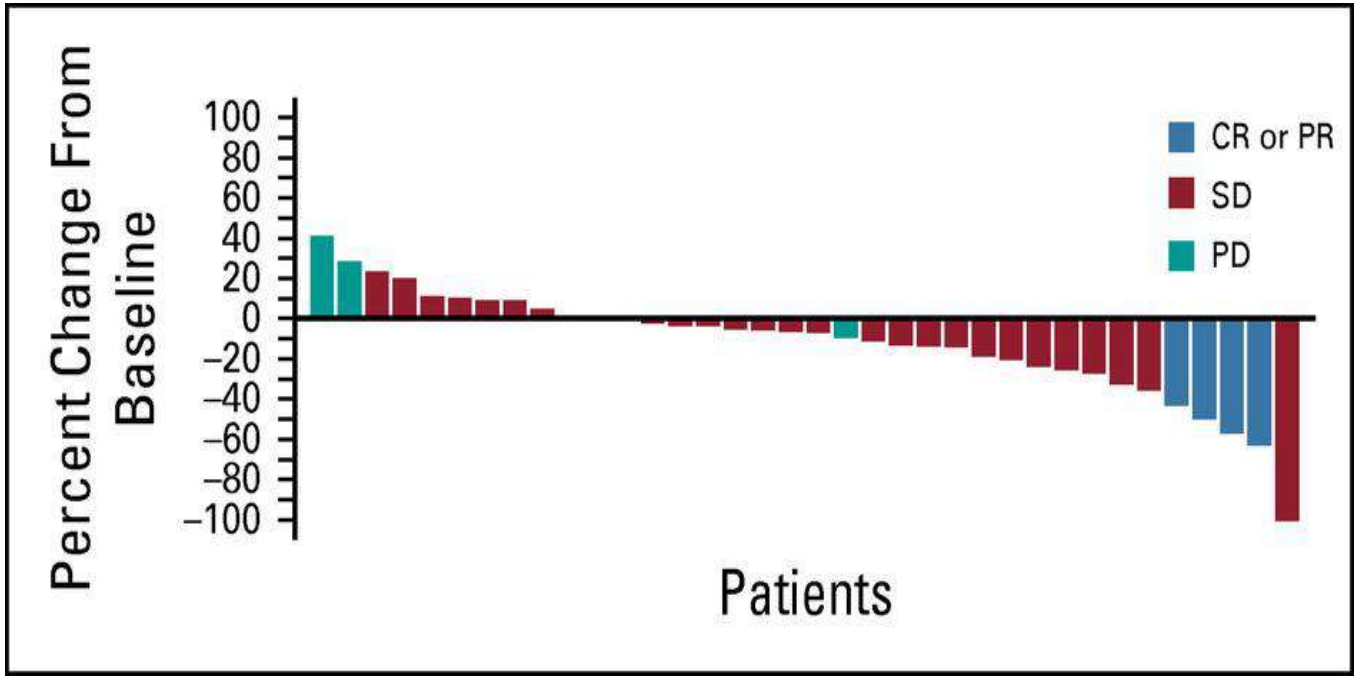


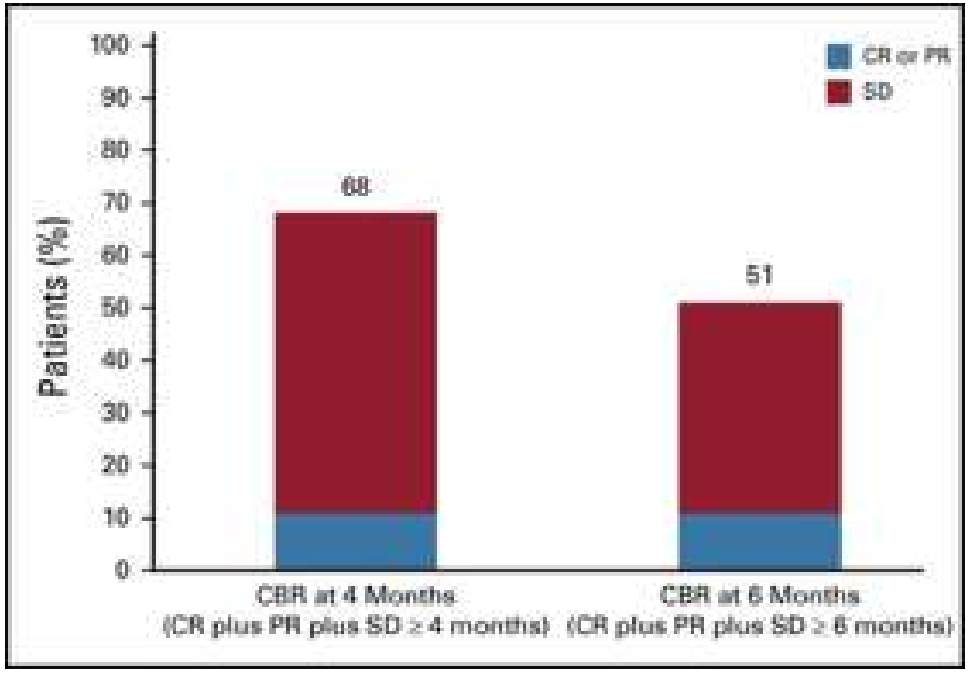
Biodistribution of 89Zr-trastuzumab and PET Imaging of HER2-Positive Lesions in Patients with Metastatic Breast Cancer

Dijkers et al, Clin Pharmacol and Therap 2010

PATRICIA STUDY

High dose trastuzumab plus pertuzumab



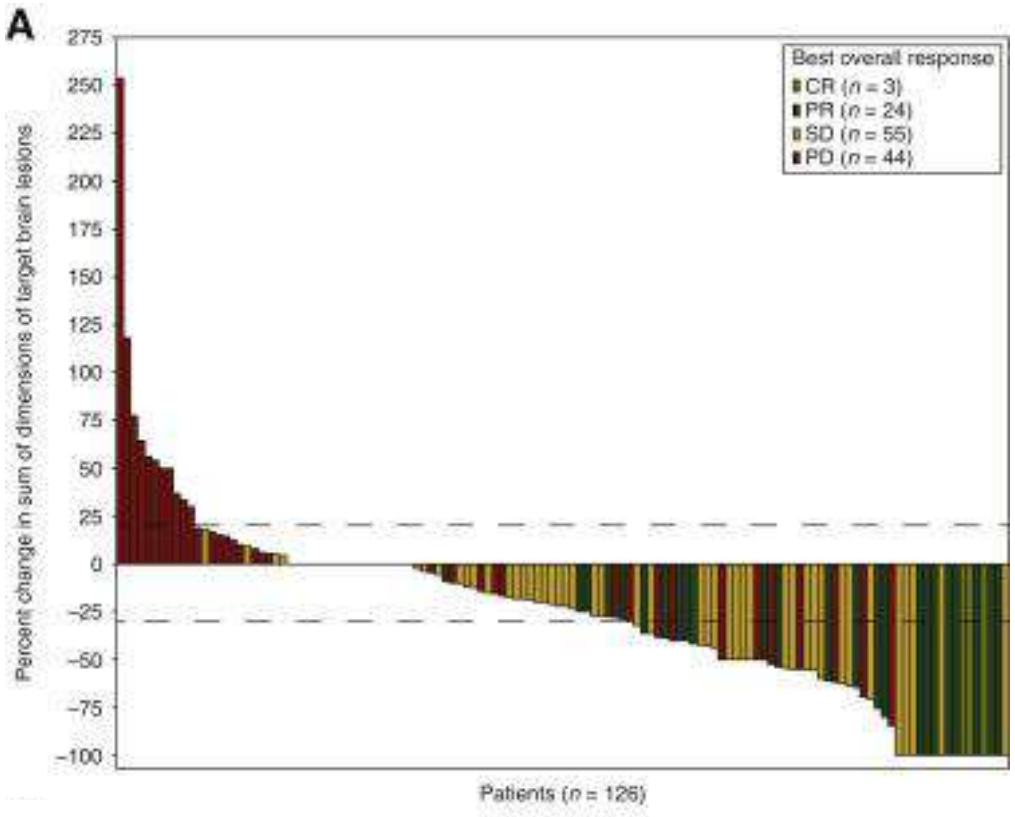


Trastuzumab 6 mg/kg IV once weekly
Pertuzumab 840 mg loading dose then 420 mg IV 3W

Lin et al, JCO 2021; Lin et al, npj Breast 2023

KAMILLA: PHASE IIIB OF T-DM1

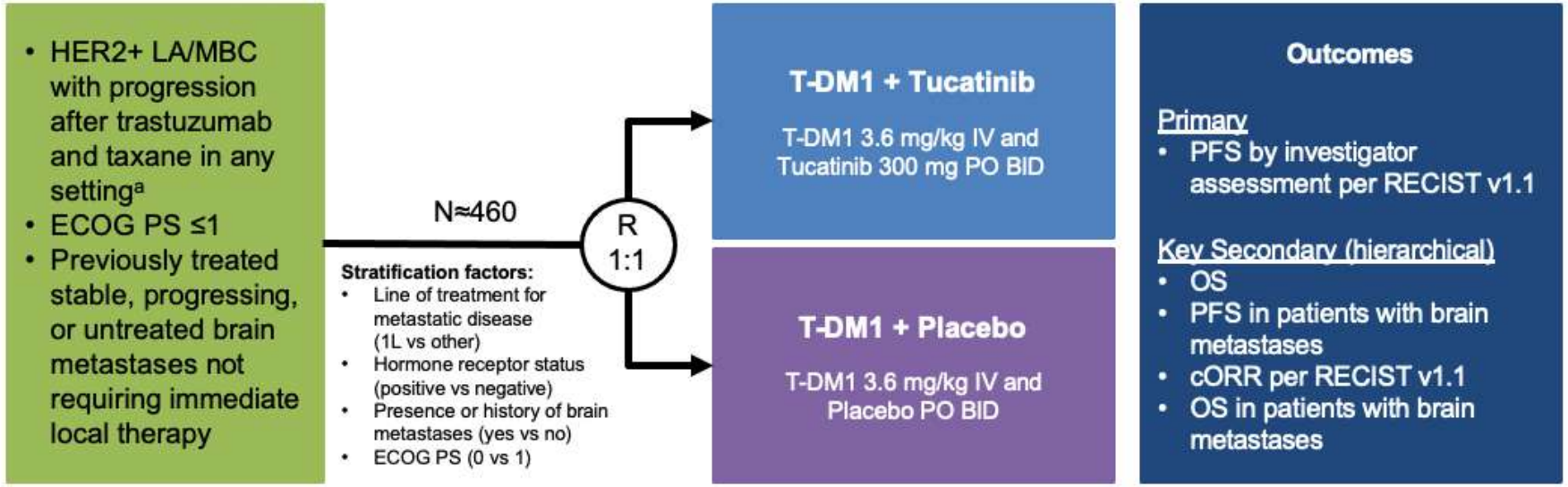
Subset analysis of patients with BM at baseline



- 398/2003 enrolled patients with BM at baseline
- In the 126 patients with measurable BM
- Best overall response (CNS and non-CNS) = 21.4%; clinical benefit rate = 42.9%
- A CNS response was observed in:
  - **32.7% of patients who received RT ≥30 days before baseline**
  - **49.3% of patients who did not receive brain radiotherapy**

Montemurro et al, Ann Oncol 2020

HERCLIMB-02: DOES TUCATINIB ADD TO T-DM1?



The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive[b].

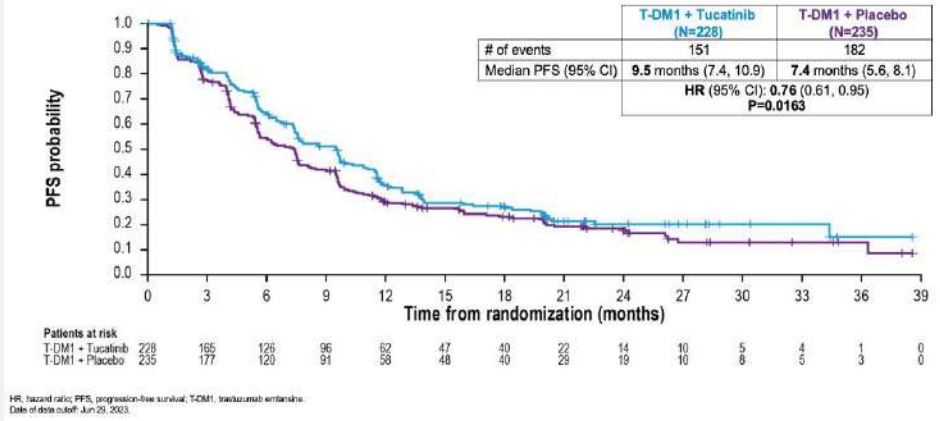
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Presence or history of brain metastases, n (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No[a]	129 (56.6)	130 (55.3)

Hurvitz et al, SABCS 2023

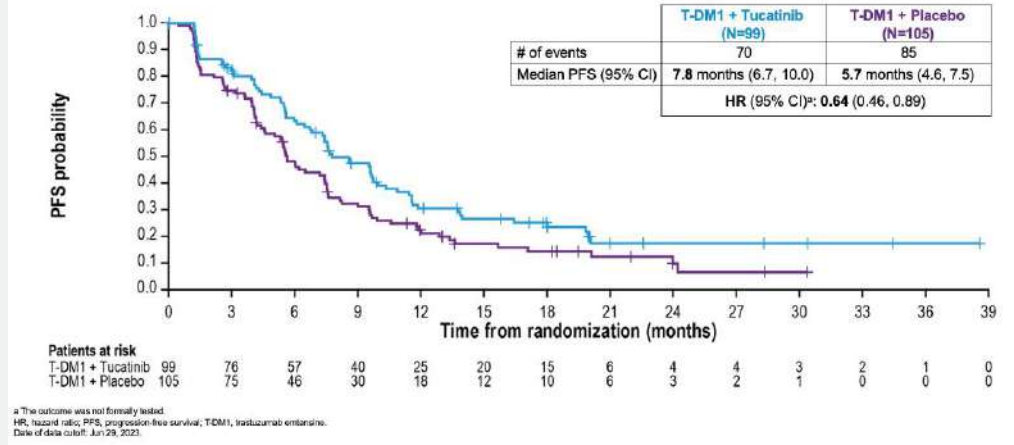
HER2CLIMB-02

Tucatinib prolongs PFS when added to T-DM1

Progression-Free Survival: ITT Population



Progression-Free Survival: BM Subset



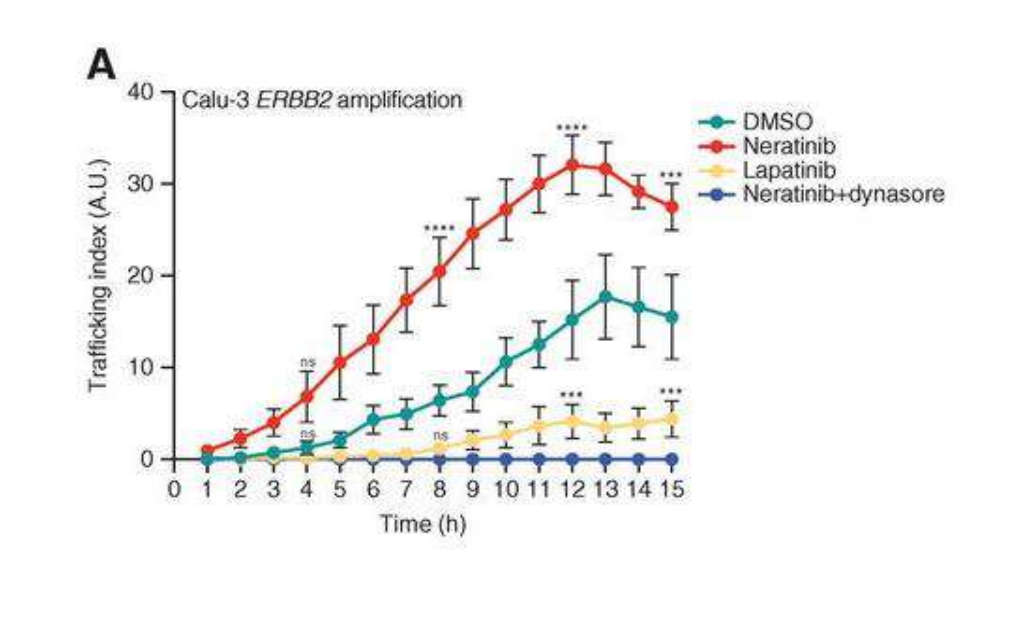
Overall ORR 36.1% vs 42.0% favoring the combination

CNS-ORR not reported

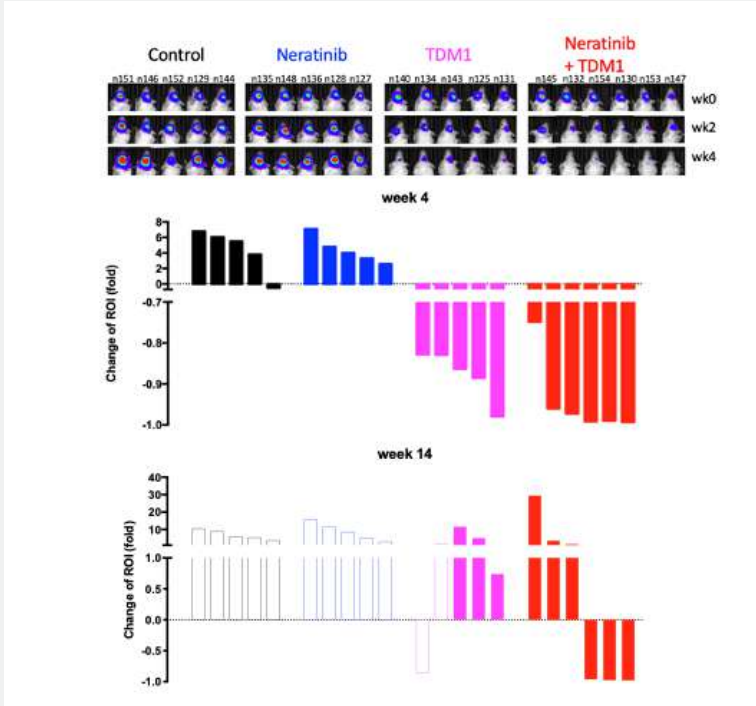
OS, no difference at median f/u 24.4 months; await more mature data

Hurvitz et al, SABCS 2023

NERATINIB MAY OVERCOME T-DM1 RESISTANCE



Li et al, Cancer Discov 2020



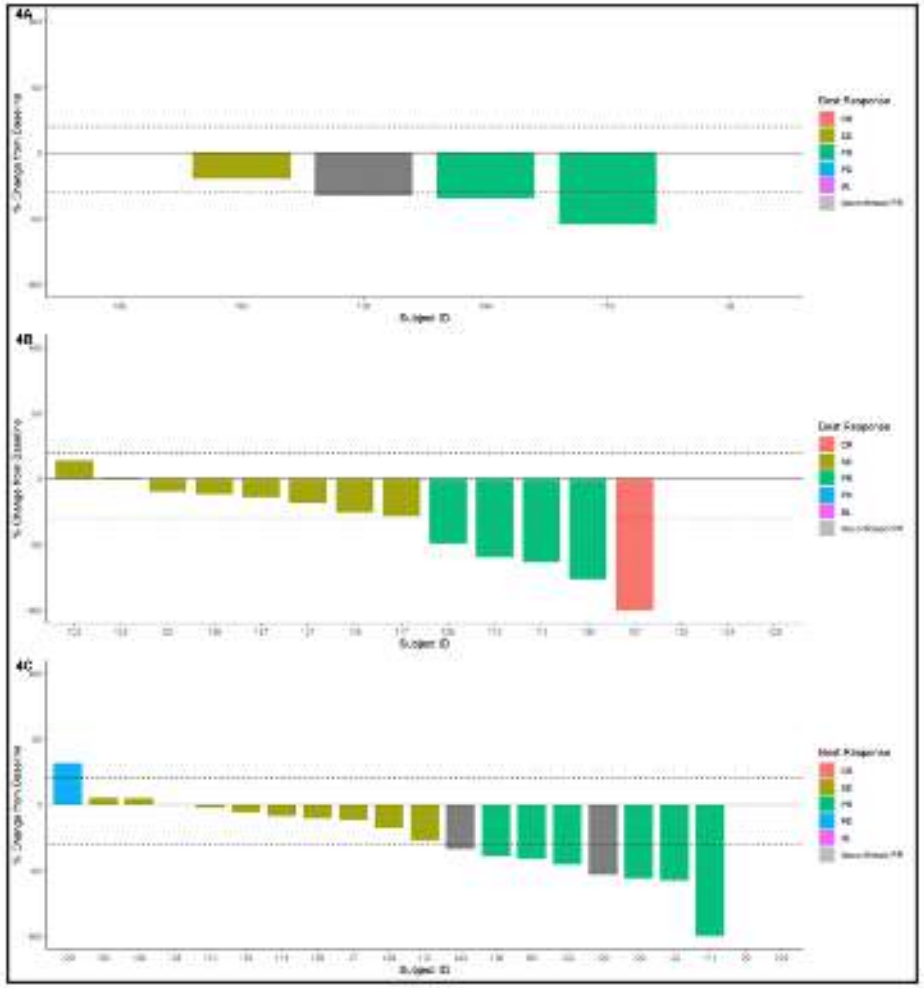
Ni et al, AACR 2021

Li et al, Cancer Discov 2020; Ni et al, AACR 2021

TBCRC 022: T-DM1 + NERATINIB FOR ACTIVE HER2+ BM

Intracranial responses observed even in pts pre-treated with T-DM1

Best Intracranial Response



Prev untreated

TDM1-naïve

TDM1 pre-treated

Freedman et al, Ann Oncol 2024

CAN WE PREVENT BRAIN METASTASES?

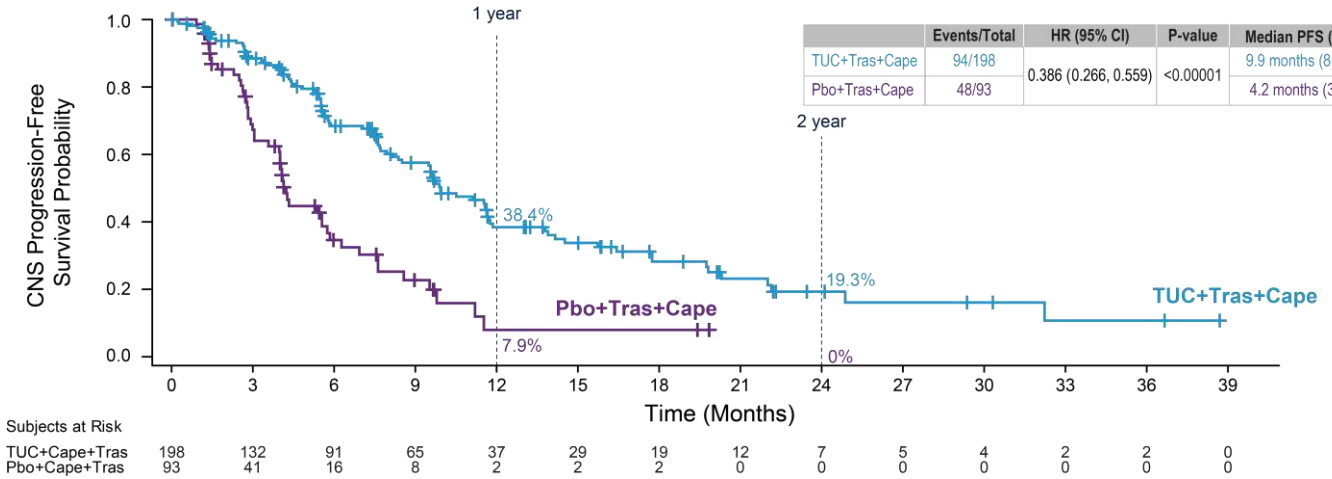
CNS RECURRENCES IN NEO/ADJUVANT HER2+ TRIALS

Trial and population		Analysis timepoint	N	Neoadjuvant population	CNS recurrence, %	
					Comparator	Treatment
Adjuvant trastuzumab Meta-analysis[2]		–	9020	N/A	1.94	2.56
ALTTO[a 17]		3 years	5190	~8%	2	2
ExteNET[b 18]	ITT	5 years	2840	26%	1.8	1.3
	HR+/≤1yr post trastuzumab	5 years	1334	27%	2.1	0.7
APHINITY[c 3] node (+) or high-risk node (–)		3 years	4805	0	1.8	1.9
No pCR post neoadjuvant treatment						
KATHERINE[d 19] high-risk		3 years	1486	N/A	4.3	5.9
ExteNET[18] HR+/≤1yr post trastuzumab		5 years	295	N/A	3.6	0.8

Lin et al, SABCS 2023

HER2CLIMB: TUCATINIB, CAPECITABINE, TRASTUZUMAB

Prolongation of CNS-PFS with tucatinib



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	94/198	0.386 (0.266, 0.559)	<0.00001	9.9 months (8.4, 11.7)
Pbo+Tras+Cape	48/93			4.2 months (3.6, 5.7)

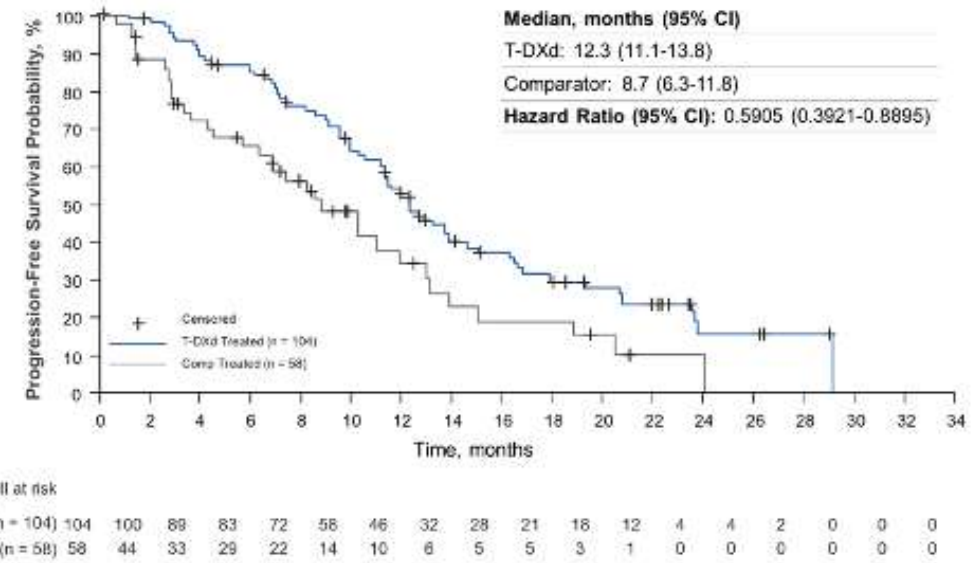
SUBGROUP	TREATMENT	EVENTS	HR (95% CI)	P value	Median CNS-PFS (95% CI)
Patients with active brain metastases	TUC+Tras+Cape	69/118	0.339 (0.215, 0.536)	<0.00001	9.6 months (7.6, 11.1)
	Pbo+Tras+Cape	35/56			4.0 months (2.9, 5.6)
Patients with treated stable brain metastases	TUC+Tras+Cape	25/80	0.406 (0.194, 0.850)	0.01	13.9 months (9.7, 24.9)
	Pbo+Tras+Cape	13/37			5.6 months (3.0, –)

Lin et al, SABCS 2021 and JAMA Oncol 2023

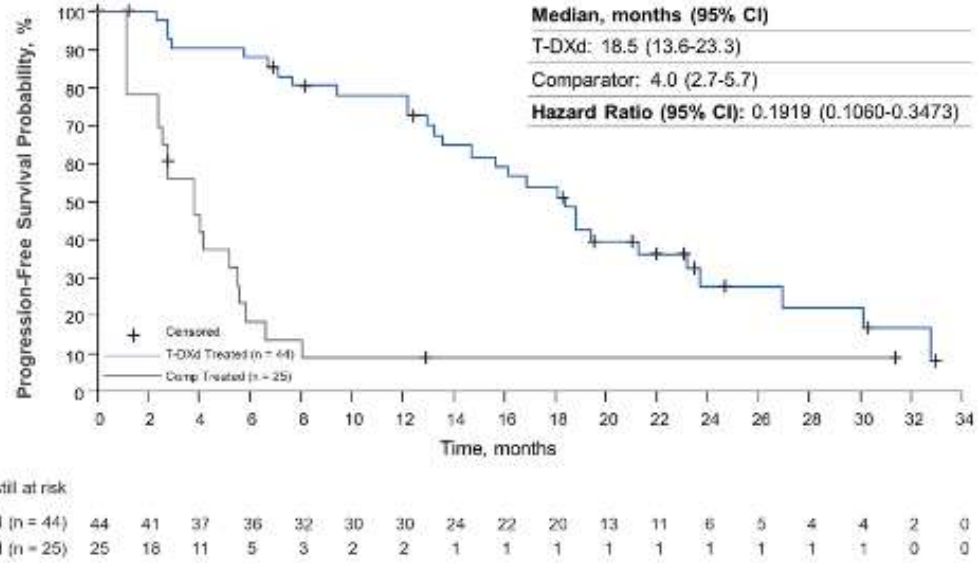
POOLED ANALYSIS OF PTS WITH BM IN DB-01, -02, AND -03

Exploratory CNS-PFS per BICR

Treated/Stable BMs



Untreated/Active BMs



- **T-DXd demonstrated a trend towards prolonged CNS-PFS over comparator, with a noticeably greater advantage for patients with untreated/active BMs**

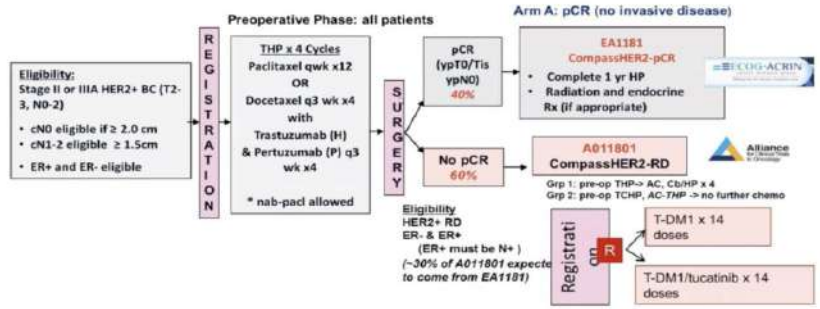
Hurvitz et al, ESMO 2023

CAN WE ACHIEVE PRIMARY PREVENTION?

CNS outcomes will be of interest to examine in these ongoing trials

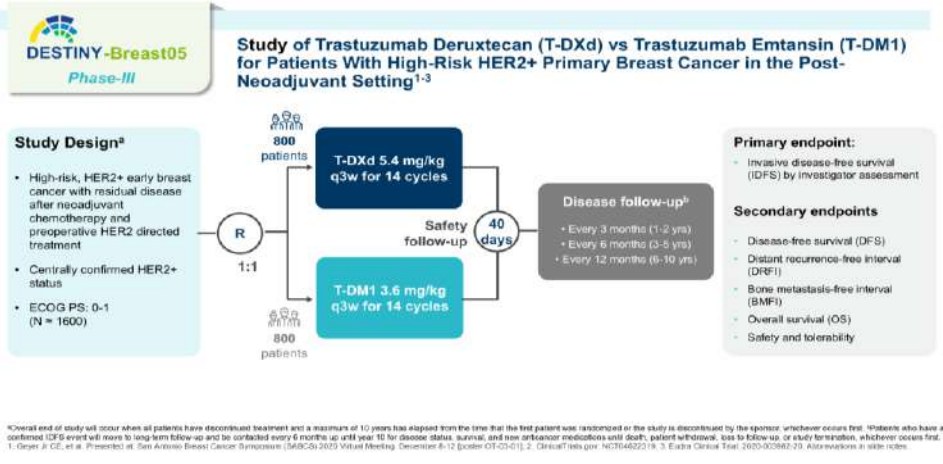
EBC

CompassHER2 (NCT04266249; NCT04457596)



https://clinicaltrials.gov/ct2/show/NCT04457596?cond=NCT04457596&draw=2&rank=1

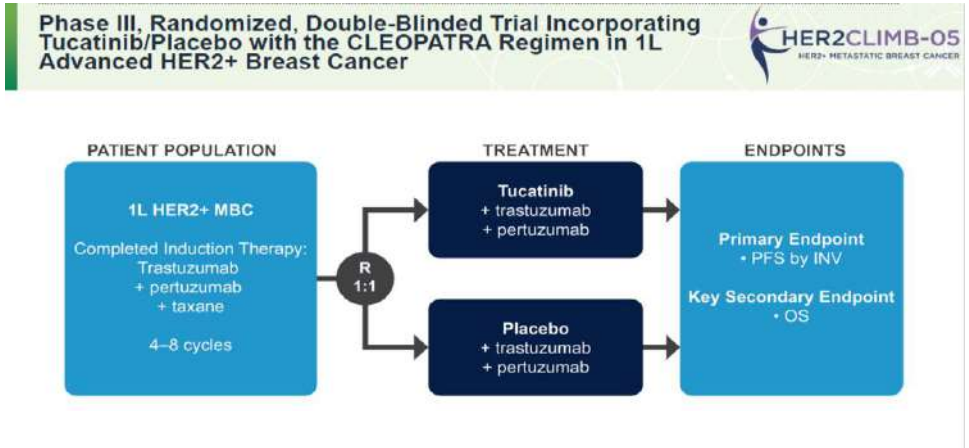
FOR REACTIVE SCIENTIFIC EXCHANGE; NOT FOR DISTRIBUTION OR PROMOTIONAL USE

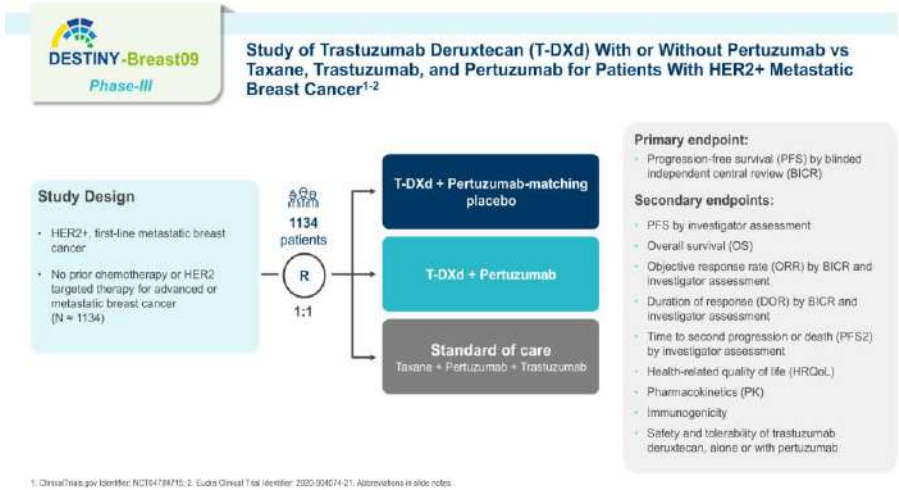


[a]Overall end of study will occur when all patients have discontinued treatment and a maximum of 10 years has elapsed from the time that the first patient was randomized or the study is discontinued by the sponsor, whichever occurs first. [b]Patients who have a confirmed IDFS event will move to long-term follow-up and be contacted every 6 months up until year 10 for disease status, survival, and new anticancer medications until death, patient withdrawal, loss to follow-up, or study termination, whichever occurs first.

1. Geyer Jr CE, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2020 Virtual Meeting; December 8-12 (poster OT-03-01). 2. ClinicalTrials.gov: NCT04622319. 3. EudraCT Clinical Trial: 2020-003882-20. Abbreviations in slide notes.

MBC





1. ClinicalTrials.gov Identifier: NCT04784715. 2. Eudra Clinical Trial Identifier: 2020-004074-21. Abbreviations in slide notes.

Slide courtesy Volkmar Muller, MD

THE IMPORTANCE OF MULTI-DISCIPLINARY CARE

Given the same information, individual patients will make different decisions

Some side effects matter more vs less to individual patients

Patients' tolerance of risk and uncertainty varies

Patients' priorities differ from each other, and in the same patient, over time

The number, size, and location of CNS lesions matter in terms of risks of radiation and risks of deferring radiation to try systemic therapy

ESMO DEEP DIVE: BREAST CANCER

THANK YOU FOR YOUR ATTENTION!

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ESMO WEBINAR SERIES

ESMO DEEP DIVE:
BREAST CANCER

OPTIMAL TREATMENT SEQUENCES AFTER GUIDELINE-BASED EARLY BREAST CANCER THERAPY

Volkmar Müller

Department of Gynecology and Breast Center
Hubertus Wald Cancer Center
University Medical Center Hamburg-Eppendorf

ESMO WEBINAR SERIES

ESMO DEEP DIVE:
BREAST CANCER

DISCLOSURE INFORMATION

- Speaker honoraria: Astra Zeneca, Daiichi-Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowissen, high5 Oncology, Medscape, Gilead, Pierre Fabre, iMED Institute
- Consultancy honoraria: Roche, Pierre Fabre, PINK, ClinSol, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Seagen, Gilead, Stemline
- Institutional research support: Novartis, Roche, Seagen, Genentech, Astra Zeneca
- Travel grants: Astra Zeneca, Roche, Pfizer, Daiichi Sankyo, Gilead

KEY REFERENCES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[2,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*

International Consensus Guidelines for Advanced Breast Cancer
ABC GUIDELINES

ABC1 ABC2 ABC3 ABC4 ABC5 ABC6

ABC7

ESMO DEEP DIVE: BREAST CANCER

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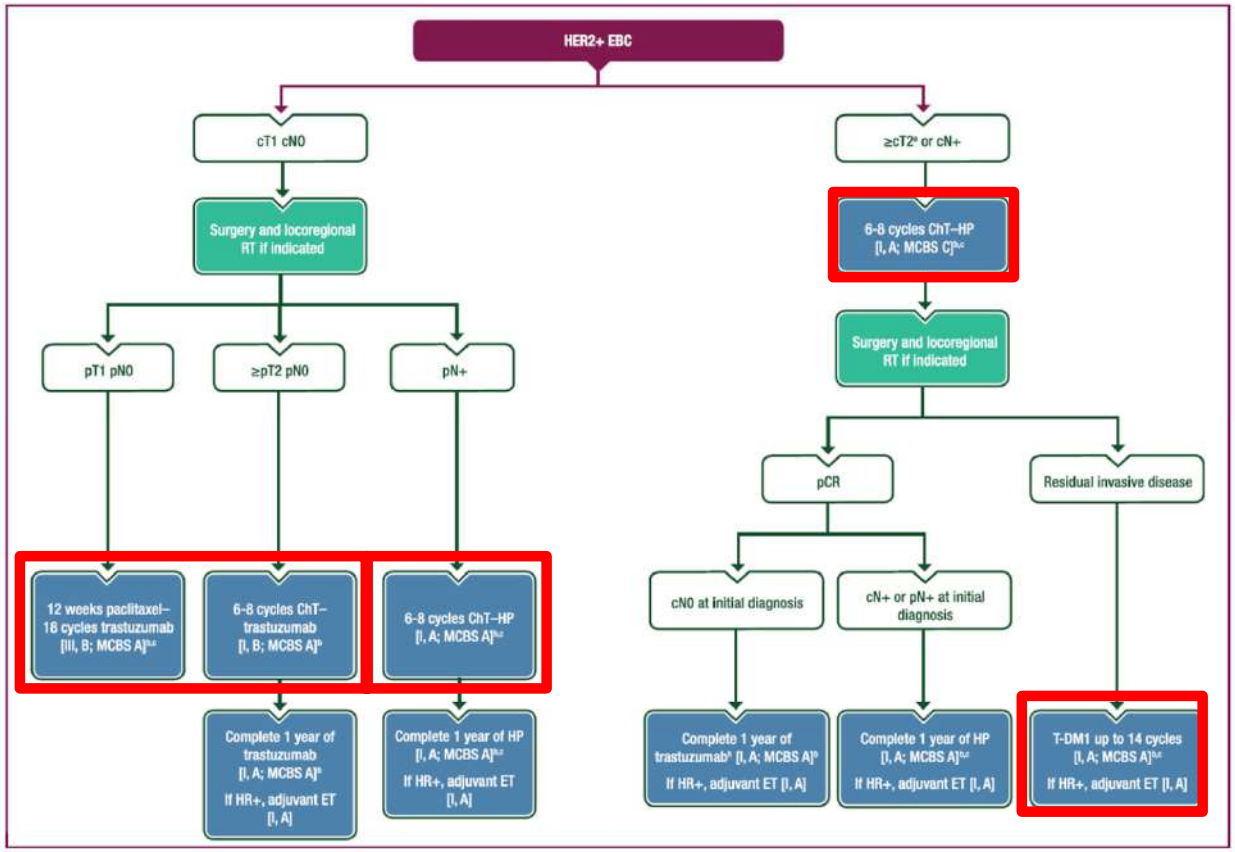
GUIDELINE-BASED THERAPY OF HER2-POS. EBC IN 2024



Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

Ann Oncol. 2024;35(2):159-182.

GUIDELINE-BASED THERAPY OF HER2-POS. EBC IN 2024

- Trastuzumab for low risk
- Trastuzumab / Pertuzumab for higher risk
- T-DM1 for non-pCR after neoadjuvant treatment
- Neratinib as option in selected HR-pos. patients

Almost all patients receive HER2-directed therapy and taxanes for EBC

OPTIMAL TREATMENT SEQUENCES AFTER GUIDELINE-BASED EARLY BREAST CANCER THERAPY

Many new options in EBC with potential impact on treatment of MBC

- With pretreatment in EBC: Re-challenge in MBC or use different compound?
- Which sequence in MBC?

ESMO DEEP DIVE:
BREAST CANCER

HOW TO TREAT IN THE METASTATIC SETTING?

1. DE-NOVO MBC (patients with MBC at initial diagnosis)

HER2CLIMB

Key Baseline Disease Characteristics in the HER2CLIMB Trial

Characteristic, n (%)		Total Population, N=612 TUC+Tras+Cape n=410	Pbo+Tras+Cape n=202
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	249 (60)	127 (63)
	ER and PR-negative	161 (40)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2, 17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Previous therapies	Trastuzumab	410 (100)	202 (100)
	Pertuzumab	409 (99.8)	201 (99.5)
	T-DM1	410 (100)	202 (100)
	Lapatinib	24 (5.9)	10 (5)

Baseline characteristics were balanced between endpoint populations and treatment arms

Murthy RK, et al. N Engl J Med 2020;382:597-609

HER2 POSTIVE DISEASE IS A RISK FACTOR FOR METASTATIC SPREAD AT INITIAL DIAGNOSIS

- HER2-positive patients had de nove MBC at initial presentation in 49.1% of cases, in comparison with 21.9%, 35.5%, and 37.6% in patients with triple-negative, luminal A-like and luminal B-like breast cancer, respectively.

- CONCLUSION: Age and breast cancer subtype are associated with the frequency of first-line MBC patients. Inclusion criteria concerning age or breast cancer subtype can influence the frequency of these patients in a selected patient population and can therefore modify the number of patients with secondary resistance to specific therapies in clinical trials.

Müller V, Hein A, Hartkopf AD, et al. Eur J Cancer. 2022;172:13-21.

ESMO DEEP DIVE: BREAST CANCER

WITH PRETREATMENT: RE-CHALLENGE OR USE NEW COMPOUND?

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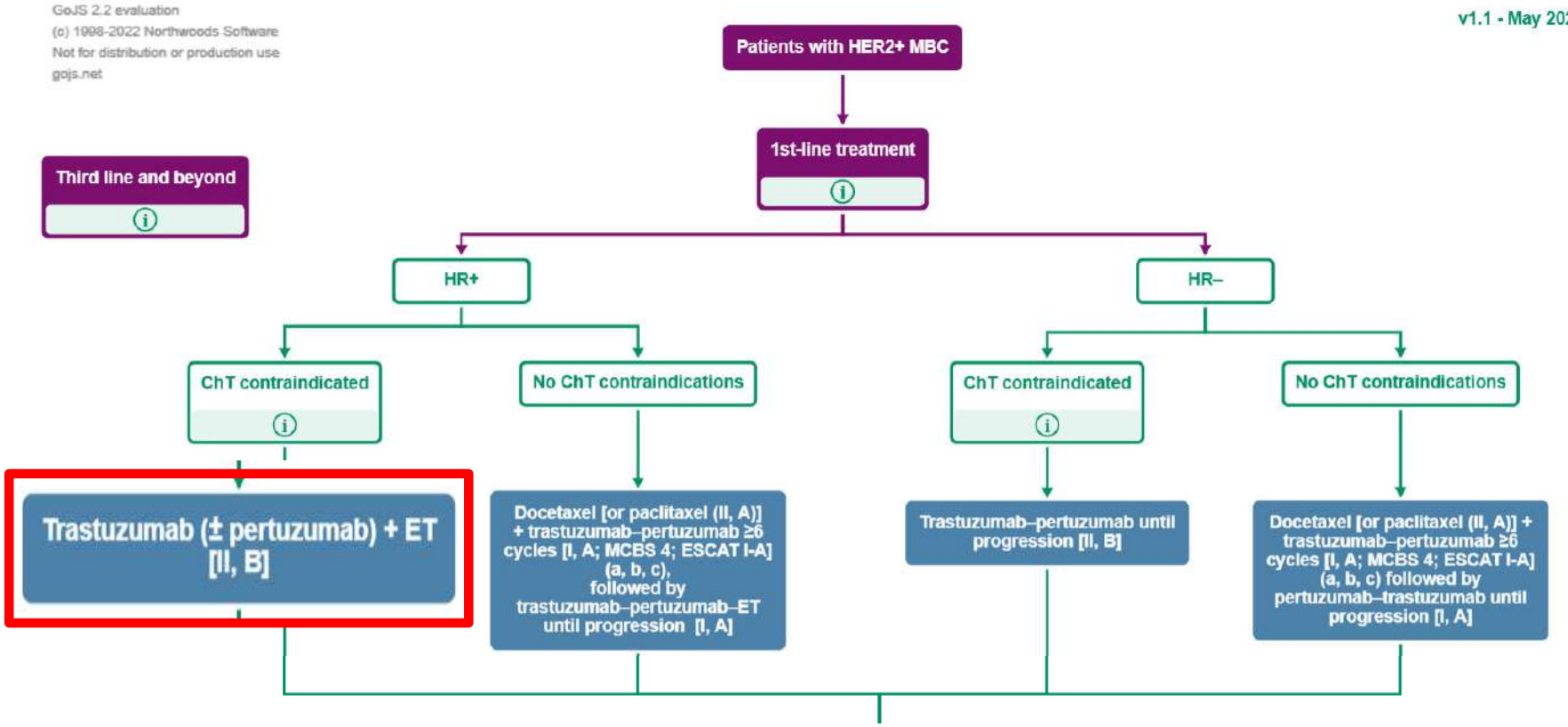
FIRST STEP: THINK ABOUT A BIOPSY

- At first diagnosis of MBC, a biopsy should be carried out to confirm histology and re-assess tumour biology (ER, PgR, HER2) [I, B]

https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

ESMO FIRST LINE TREATMENT



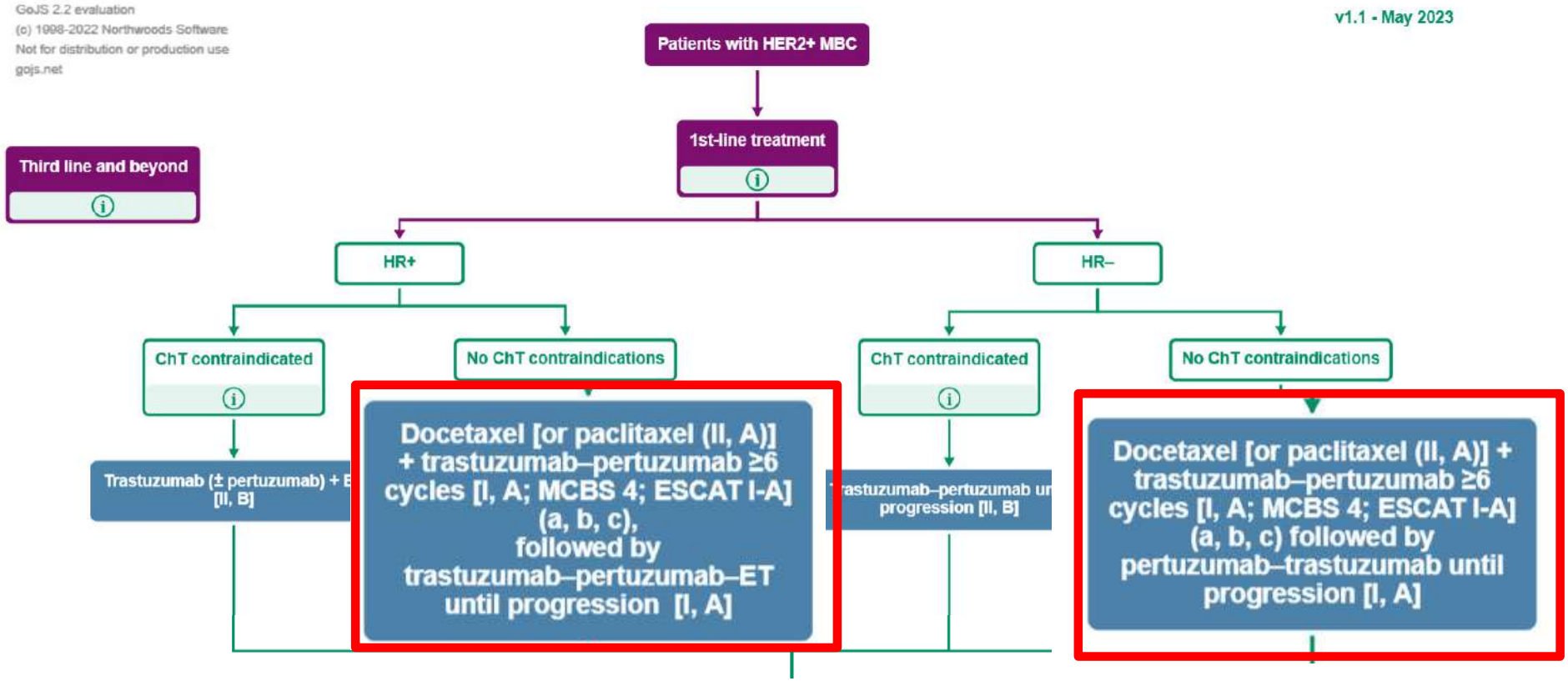
https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

IS THERE A ROLE FOR HER2-TARGETING THERAPY WITHOUT CHEMOTHERAPY?

- TAnDEM (n=207): Trastuzumab with anastrozole as first-line treatment. Median PFS trastuzumab combined with anastrozole 4.8 and 2.4 months with anastrozole monotherapy (HR = 0.63; p = 0.0016)
- eLEcTRA (n=56): Median time to progression with letrozole 3.3 months compared to 14.1 months with letrozole plus trastuzumab
- PERTAIN (n=258): First-line pertuzumab/trastuzumab or trastuzumab each combined with AI. Some patients in both groups received induction chemotherapy followed by endocrine-targeted therapy after chemotherapy. Median PFS was 18.9 months in the pertuzumab plus trastuzumab arm and 15.80 months in the trastuzumab arm (HR, 0.65; p = 0.0070)
- **No OS advantage for addition of HER2-directed therapy to endocrine therapy**

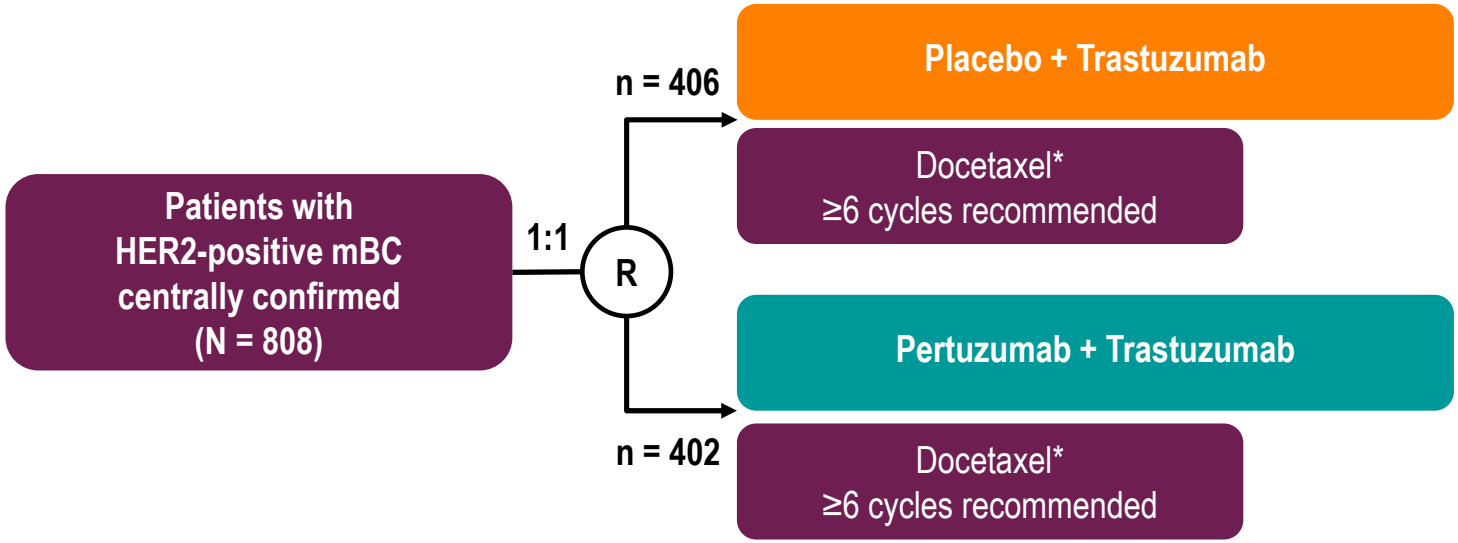
Kaufman B, J Clin Oncol 2009; 27: 5529–5537 Huober J, Breast 2012; 21: 27–33
Arpino G, Clin Cancer Res. 2023;29:1468-76

ESMO FIRST LINE TREATMENT



https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline

CLEOPATRA IS A PHASE III STUDY OF PERTUZUMAB / TRASTUZUMAB 1L MBC



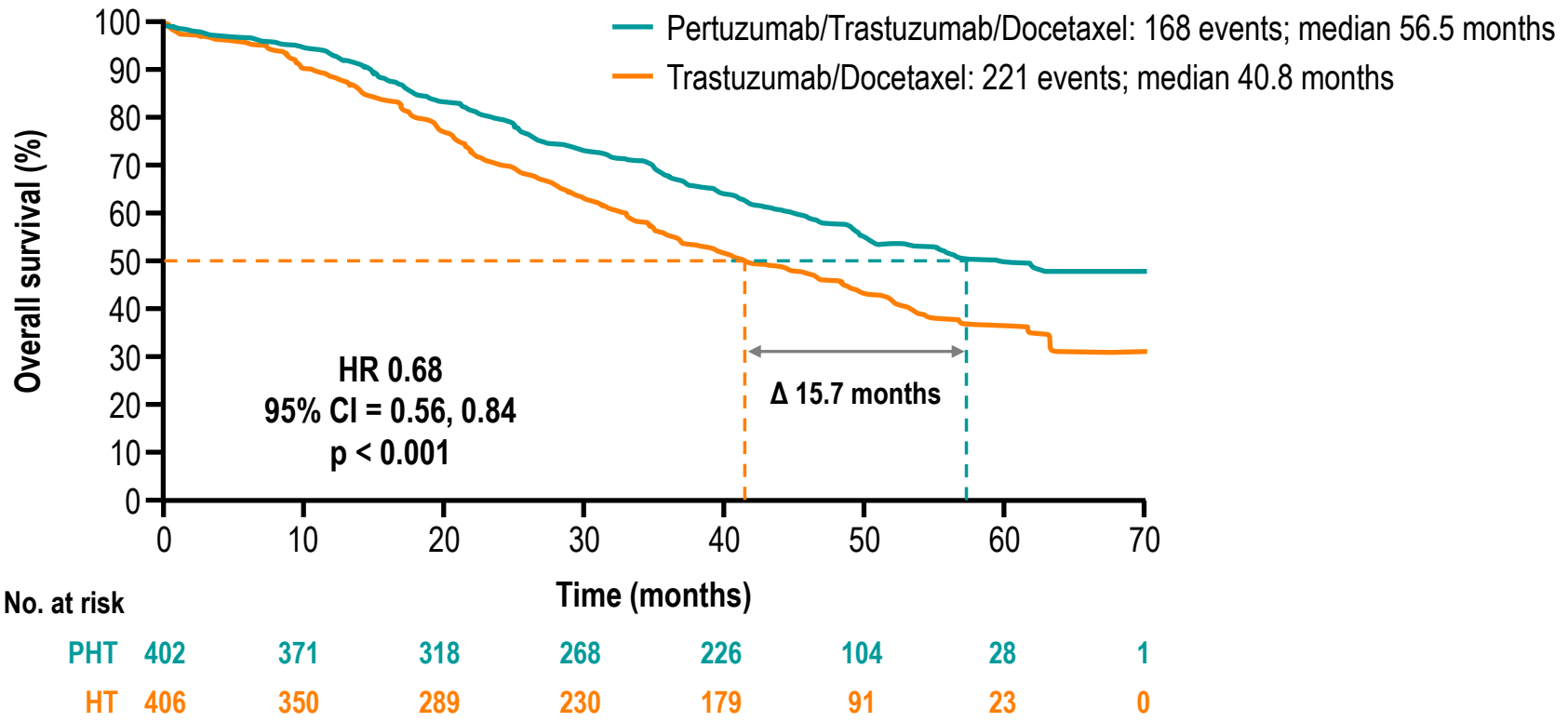
*<6 cycles allowed for unacceptable toxicity or PD;
>6 cycles allowed at investigator's discretion

- **Primary endpoint:** Independently-assessed PFS
- **Secondary endpoints:** Investigator-assessed PFS, OS, ORR, safety (monitored by an independent DMC and CRC)

Baselga J, et al. N Engl J Med 2012; 366:109–119.

CRC, clinical review committee; DMC, data monitoring committee; PD, progressive disease; PFS, progression-free survival; mBC, metastatic breast cancer ORR, overall response rate; OS, overall survival.

FINAL OS ANALYSIS*:



* Data cut-off: February 2014.

CI, confidence interval; H, Herceptin; HR, hazard ratio; OS, overall survival; P, PERJETA; T, docetaxel.

Swain SM, et al. N Engl J Med 2015; 372:724–734.

CLEOPATRA
PRIOR THERAPY FOR BREAST CANCER

Only ≈ 50% of patients in Cleopatra received (neo)adjuvant chemotherapy and only 10/12% Trastuzumab

	HT (n = 406)	PHT (n = 402)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	192 (47.3)	184 (45.8)
No	214 (52.7)	218 (54.2)
Components of (neo)adjuvant therapy,* n (%)		
Anthracycline	164 (40.4)	150 (37.3)
Hormones	97 (23.9)	106 (26.4)
Taxane	94 (23.2)	91 (22.6)
Trastuzumab	41 (10.1)	47 (11.7)

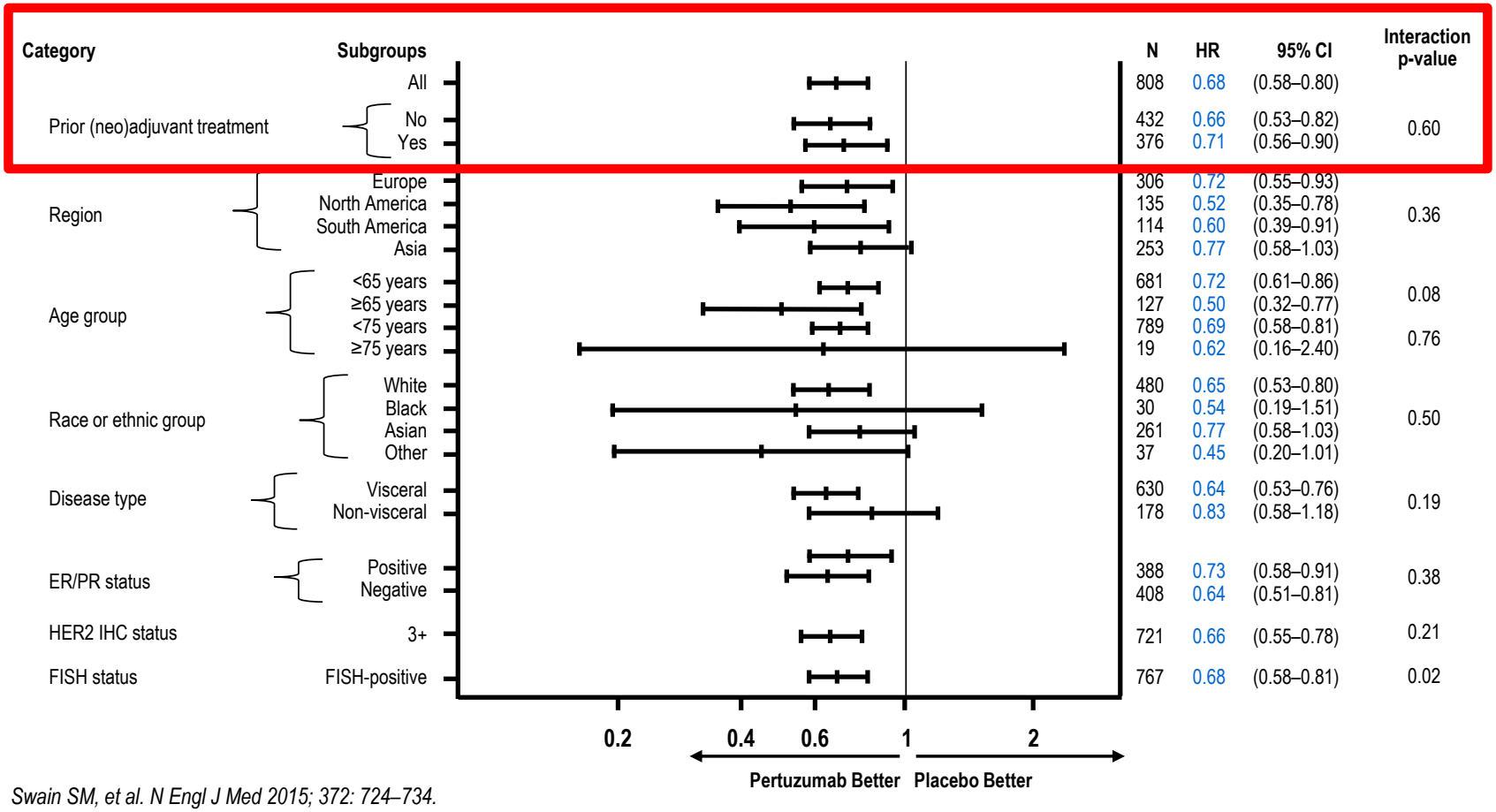
Among patients who had received (neo)adjuvant therapy (n = 376), 21.4% and 25.5% had received trastuzumab in HT and PHT groups respectively (see notes)

* Numbers add up to more than 100% because patients could have received more than one therapy.

Baselga J, et al. N Engl J Med 2012; 366:109–119.

CLEOPATRA

Investigator-assessed PFS subgroup analysis (at time of final OS analysis)



Swain SM, et al. N Engl J Med 2015; 372: 724–734.

Data cut-off: February 2014; ER, oestrogen receptor; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry OS, overall survival; PFS, progression-free survival; PR, progesterone receptor.

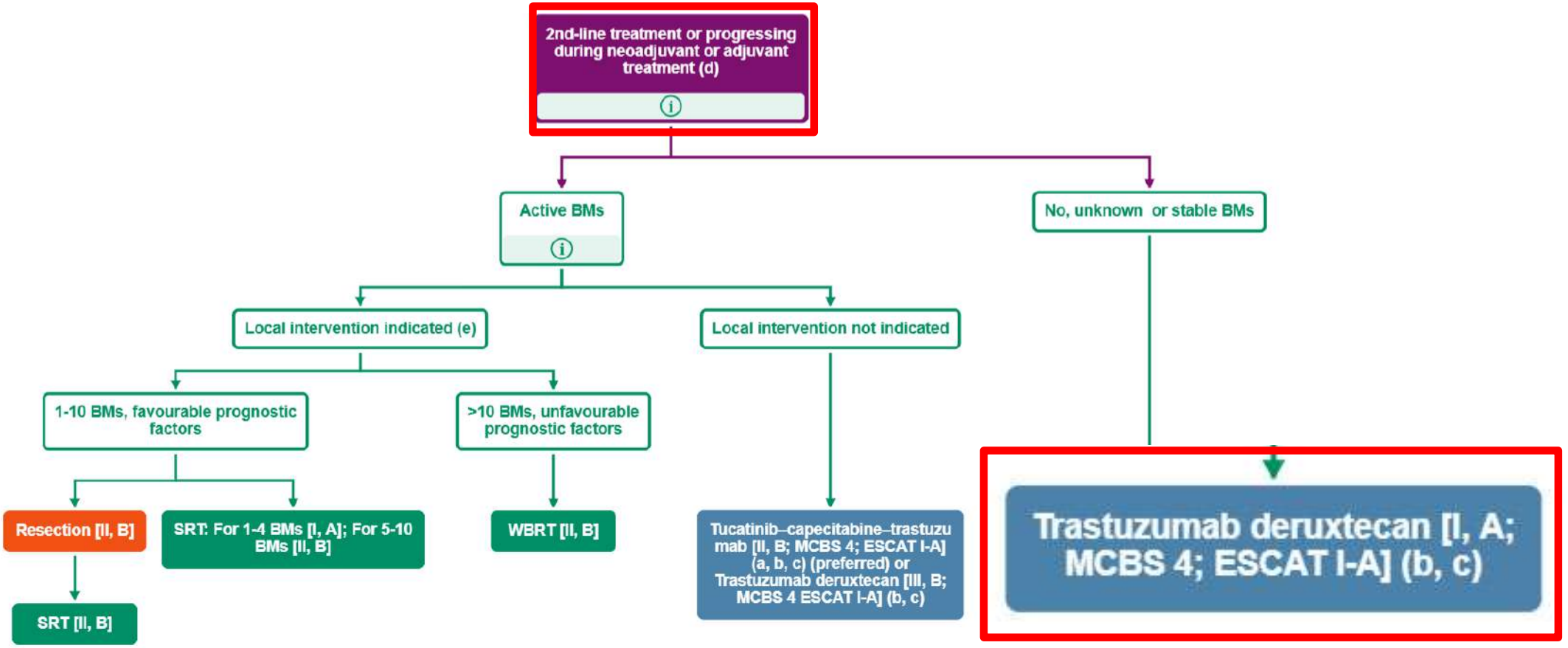
PRECIOUS-STUDY: PERTUZUMAB AFTER PERTUZUMAB EVIDENCE FROM THE METASTATIC SETTING

- 219 patients with pretreated with trastuzmumab and pertuzumab were randomized to pertuzumab, trastuzumab plus chemotherapy or trastuzumab plus chemotherapy
- Median PFS was 5.3 with PTC and 4.2 months with TC (HR 0.76 p = 0.022)
- Progression-free survival was improved by adding pertuzumab in all prespecified subgroups
- Conclusion: “Pertuzumab retreatment contributes to disease control for HER2-positive locally advanced or metastatic breast cancer previously treated with pertuzumab-containing regimens”

Yamamoto Y, et al.: Pertuzumab retreatment for HER2-positive advanced breast cancer: A randomized, open-label phase III study (PRECIOUS). Cancer Science. 2022;113:3169-79

AFTER TRASTUZUMAB/PERTUZUMAB?

… and patients progressing during or shortly after adjuvant treatment?

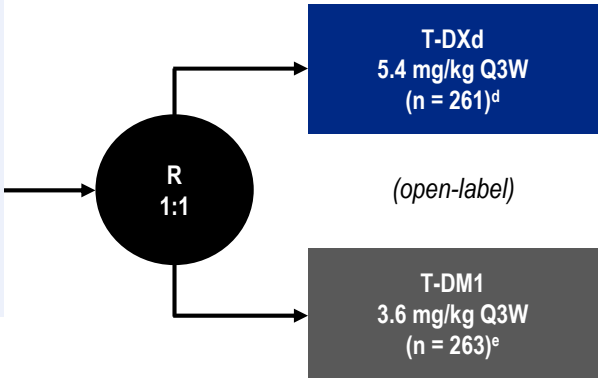


DESTINY-Breast03: Study Design

AN OPEN-LABEL, MULTICENTER, PHASE 3 STUDY (NCT03529110)[1-6]

Patients (N = 524)

- **Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and taxane[b]**
- Patients with clinically inactive/asymptomatic BMs were allowed if they did not require treatment with corticosteroids or anticonvulsants[c]
  - ≥2 weeks must have elapsed since the receipt of whole-brain radiotherapy or stereotactic radiation therapy, and radiotherapy during the treatment period was prohibited



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS[f]

Secondary endpoints
- ORR (BICR and investigator)
- DoR (BICR)
- PFS (investigator)
- Safety
- HEOR outcomes (PROs and hospitalization rates)

Exploratory subgroup analysis

Disease history
- De novo or recurrent metastatic disease at diagnosis
- Presence or absence of visceral disease at baseline
- Presence or absence of BM at baseline

Setting for 1 prior line of therapy[g]
- Metastatic
- (Neo)adjuvant (early progression)

Prior anti-HER2 therapy
- 1 line, ≥2 lines, 1 or 2 lines, ≥3 lines
- Prior pertuzumab

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

- BMs were measured at baseline by CT or MRI and BM progression was monitored throughout the study

Eligible patients had HER2- positive unresectable or metastatic breast cancer that was previously treated with trastuzumab and a taxane in the advanced or metastatic setting or **progressed during or within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab and a taxane**

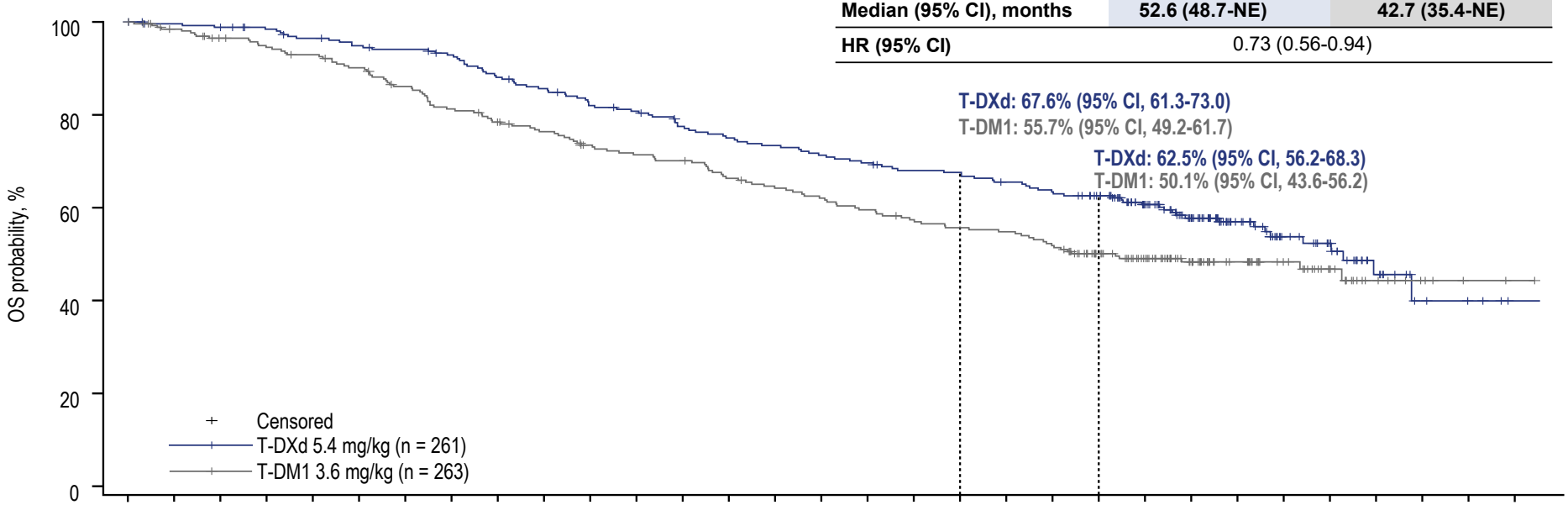
This figure was reprinted from *Ann Oncol*, Vol. 34 (7). Curigliano G et al. Patient-reported outcomes and hospitalization data in patients with HER2-positive metastatic breast cancer receiving trastuzumab deruxtecan or trastuzumab emtansine in the phase III DESTINY-Breast03 study, 569-577. Copyright (2023), with permission from Elsevier.
[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing neoadjuvant or adjuvant therapy involving trastuzumab or a taxane. [c]The initial version of the protocol allowed patients with previously locally untreated BMs to be enrolled; however, following the protocol amendment, prior local therapy to BM became mandatory. [d]4 patients were randomly assigned but not treated. [e]2 patients were randomly assigned but not treated. [f]80% powered at 2-sided significance level of 5%. [g]In patients with exactly 1 prior line of therapy in the metastatic setting, excluding hormone therapy.

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154. 2. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154 [supplement]. 3. Cortés J et al. Presented at: ESMO Virtual Congress 2022; September 9-13, 2022. Poster 236P. 4. Curigliano G et al. Presented at: European Society for Medical Oncology Breast Cancer 2022; May 3-5, 2022; Berlin, Germany. Presentation 163O. 5. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 6-10, 2022; San Antonio, TX, USA. Presentation GS2-02. 6. Hurvitz SA et al. *Lancet.* 2023;401:105-117.

DESTINY-Breast03: November 20, 2023

OVERALL SURVIVAL[1,2]

	T-DXd 5.4 mg/kg n = 261	T-DM1 3.6 mg/kg n = 263
Median (95% CI), months	**52.6 (48.7-NE)**	**42.7 (35.4-NE)**
HR (95% CI)	0.73 (0.56-0.94)	



Patients still at risk																															
T-DXd 5.4 mg/kg (n = 261)	261	257	255	250	244	239	236	231	219	212	202	198	188	182	178	173	169	163	162	156	151	143	115	91	60	40	32	15	6	4	1
T-DM1 3.6 mg/kg (n = 263)	263	253	244	238	233	225	213	201	193	185	175	170	167	157	151	146	140	134	130	128	121	100	85	63	45	33	21	10	5	2	1

Crosses indicate where data were censored, number of patients censored are not stated.

1. Cortés J et al. Nat Med. 2024; doi:10.1038/s41591-024-03021-7. 2. Hamilton E et al. Presented at: ASCO Annual Meeting; May 31- June 4, 2024; Chicago, IL, USA. Poster 1025.

DESTINY-Breast03: November 20, 2023

PRIOR THERAPIES[1,2]

Characteristic	T-DXd n = 261	T-DM1 n = 263
Any previous systemic cancer therapy,[a] n (%)	260 (99.6)	262 (99.6)
Trastuzumab	**260 (99.6)**	**262 (99.6)**
T-DM1	1 (0.4)	0
Pertuzumab	**162 (62.1)**	**158 (60.1)**
Taxane and trastuzumab	260 (99.6)	262 (99.6)
Other anti-HER2 therapy	42 (16.1)	38 (14.4)
HER2 TKI	42 (16.1)	36 (13.7)
Other anti-HER2 antibody or ADC	2 (0.8)	3 (1.1)
Hormone therapy	109 (41.8)	112 (42.6)
Other systemic therapy not hormone or HER2-directed	183 (70.1)	177 (67.3)
Number of prior lines of therapy in the metastatic setting, median (range)	2 (0-16)	2 (0-15)
Previous treatment for metastatic breast cancer, n (%)	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting,[b] n (%)		
0	1 (0.4)	1 (0.4)
1	108 (41.4)	102 (38.8)
2	60 (23.0)	64 (24.3)
3	44 (16.9)	45 (17.1)
4	15 (5.7)	23 (8.7)
≥5	33 (12.6)	28 (10.6)

[a]Two patients (one in each treatment group) were randomized in error and the previous cancer systemic therapy case report form was not completed. One patient who had previously received treatment with T-DM1 was enrolled in error in the T-DXd group.[3] **[b]Includes regimens indicated for advanced/metastatic disease or early progression within 6 months of regimen for (neo)adjuvant (12 months for pertuzumab).**

1. Cortés J et al. Nat Med. 2024; doi:10.1038/s41591-024-03021-7. 2. Hamilton E et al. Presented at: ASCO Annual Meeting; May 31- June 4, 2024; Chicago, IL, USA. Poster 1025 [supplement]. 3. Cortés J et al. N Engl J Med. 2022;386:1143-1154.

DESTINY-Breast03: November 20, 2023

POST-TRIAL ANTICANCER SYSTEMIC TREATMENT

	T-DXd n = 261	T-DM1 n = 263
Patients who discontinued study treatment[a], n (%)	207 (80.5)	251 (96.2)
Patients assigned to undergo surgery[b]	6 (2.9)	15 (6.0)
Patients assigned to receive radiation treatment[b]	26 (12.6)	43 (17.1)
Patients assigned to receive post-trial anticancer systemic treatment[b]	144 (69.6)	198 (78.9)
Type of post-trial anticancer systemic treatment[c], n (%)		
Trastuzumab	57 (39.6)	103 (52.0)
T-DXd	12 (8.3)	64 (32.3)
T-DM1	75 (52.1)	26 (13.1)
Pertuzumab	17 (11.8)	31 (15.7)
Taxane	22 (15.3)	38 (19.2)
Taxane and trastuzumab	12 (8.3)	33 (16.7)
Other HER2-directed therapy	57 (39.6)	102 (51.5)
HER2-directed TKI	52 (36.1)	95 (48.0)
Other HER2-directed antibody or ADC	13 (9.0)	23 (11.6)
Hormone therapy	29 (20.1)	41 (20.7)
Other systemic therapy	100 (69.4)	158 (79.8)

[a]The denominator for calculating the percentage was the number of patients who received at least 1 dose of study treatment (safety analysis set) in the T-DXd or T-DM1 group. [b]The denominator for calculating the percentage was the number of patients who discontinued study treatment in the T-DXd or T-DM1 group. [c]The denominator for calculating the percentage was the number of patients who were assigned to any anticancer systemic treatment in the T-DXd or T-DM1 group. Patients could have received more than one type of therapy.

Cortés J et al. Nat Med. 2024; doi:10.1038/s41591-024-03021-7. Cortés J et al. Nat Med. 2024; [extended data]; doi:10.1038/s41591-024-03021-7. Hamilton E et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA. Poster 1025.

ESMO DEEP DIVE:
BREAST CANCER

EFFICACY OF TRASTUZUMAB DERUXTECAN AFTER T-DM1?

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DESTINY-Breast02

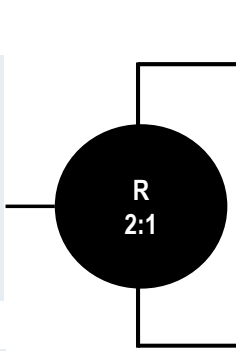
Randomized phase 3, open-label, multicenter study (NCT03523585

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



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)

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

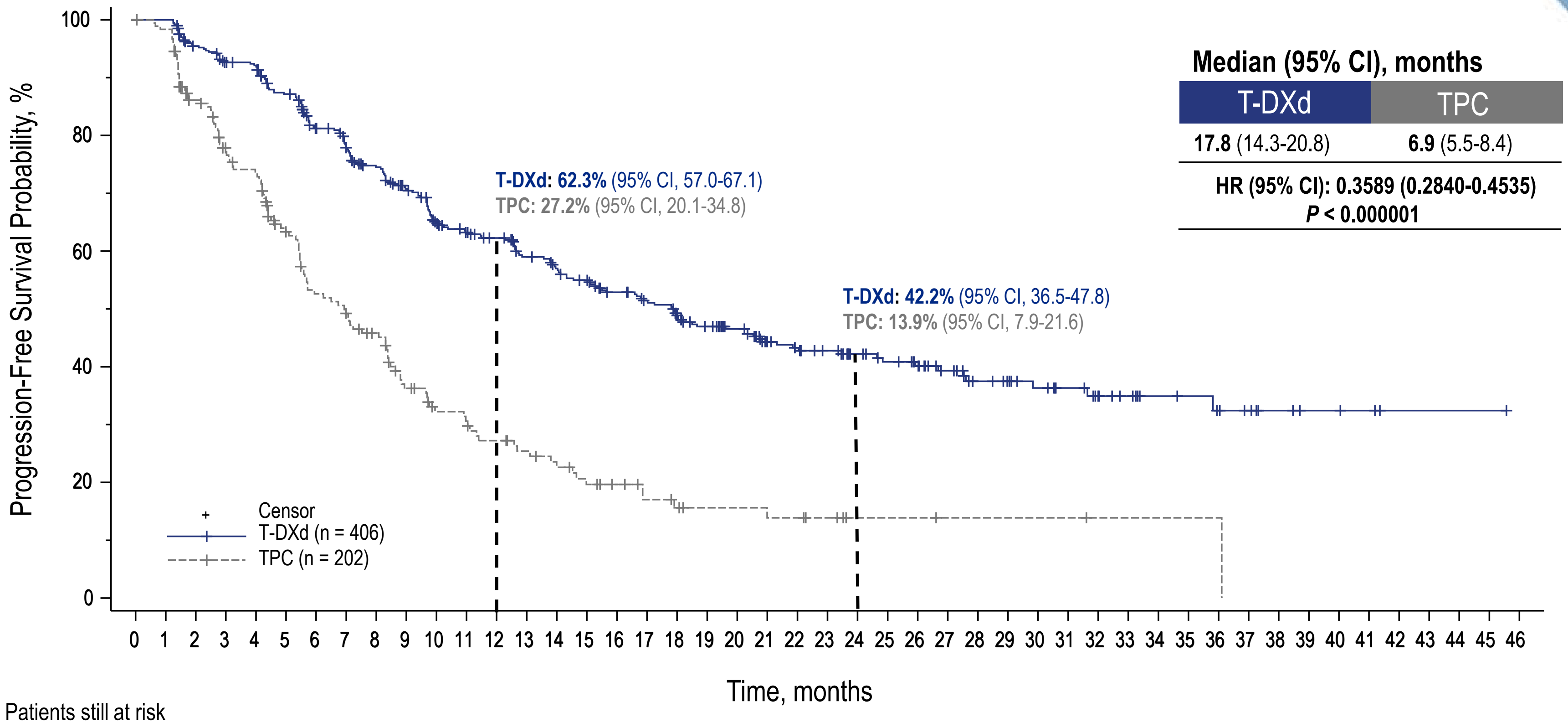
Protocol-prespecified statistical analysis plan

- 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

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1.
[c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

PRIMARY ENDPOINT: PFS BY BICR

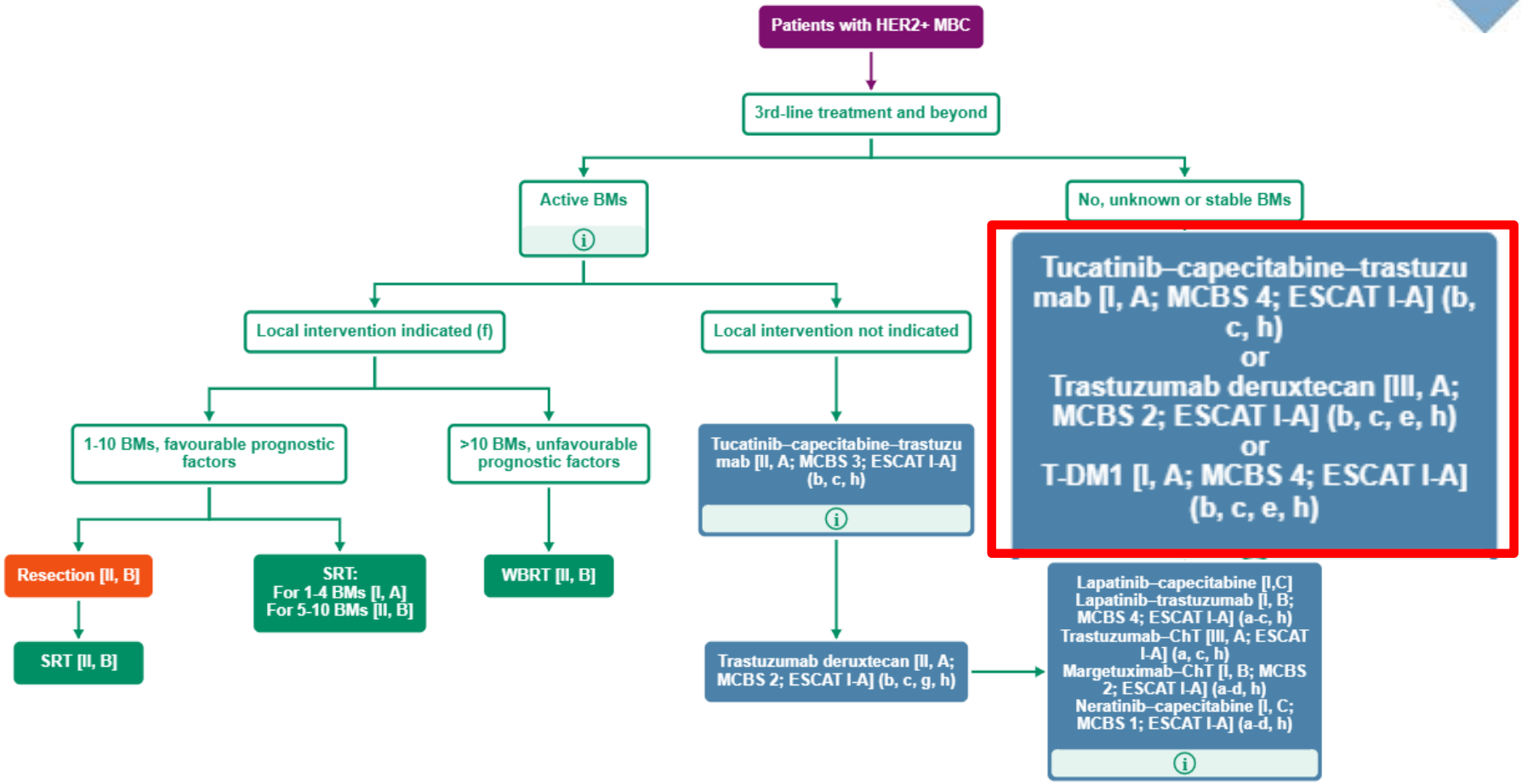


Patients still at risk

T-DXd (406)	406	400	374	359	355	330	296	278	260	239	213	203	194	179	170	161	149	141	132	119	109	88	83	76	65	60	55	47	38	35	31	27	23	19	15	14	12	10	6	4	4	3	1	1	1	1	0
TPC (202)	202	180	148	126	118	95	78	72	64	48	39	37	32	28	24	20	17	13	11	9	9	8	8	6	3	3	3	2	2	2	2	2	1	1	1	1	1	0									

BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

What to do after two or more lines?



HER2CLIMB TRIAL DESIGN

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- **Prior treatment with trastuzumab, pertuzumab, and T-DM1**
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab[a] + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab[a] + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

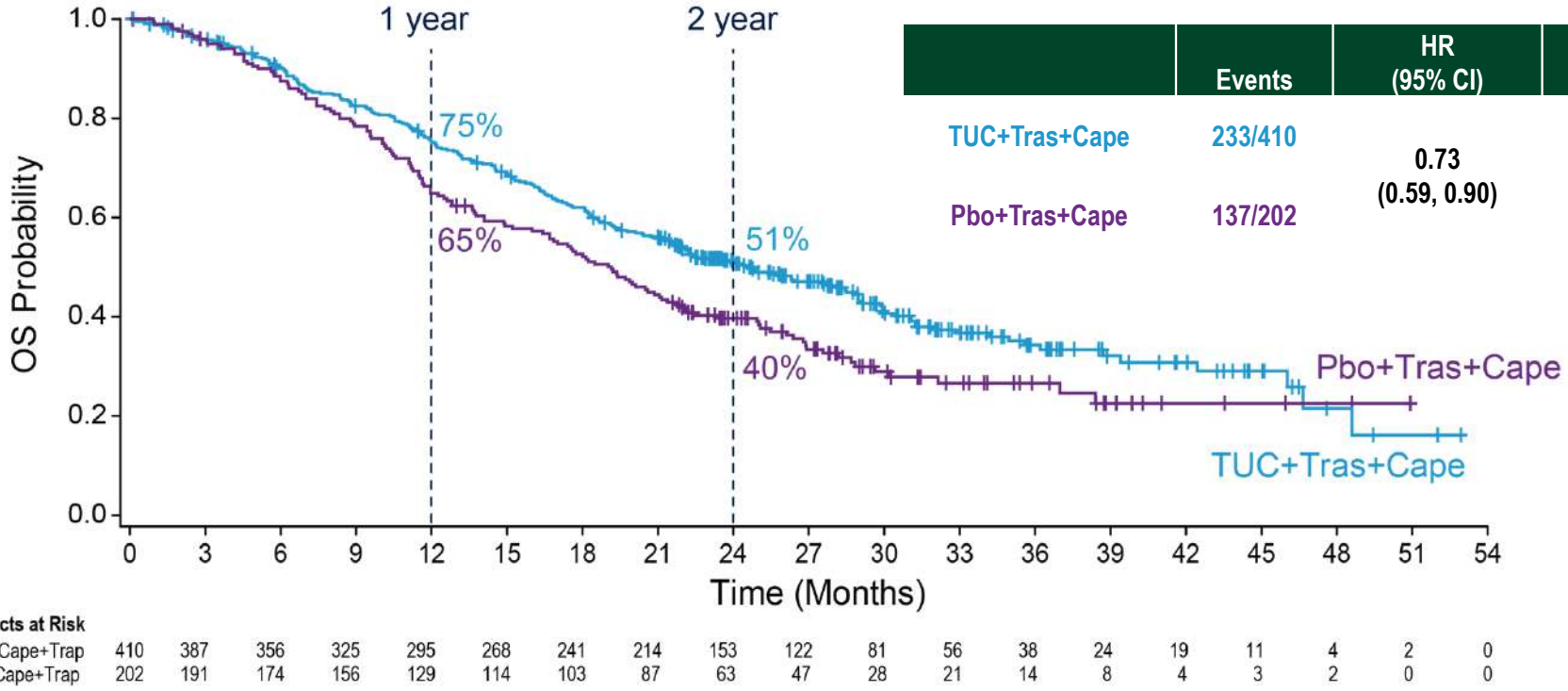
Primary Endpoint: PFS in 480 patients; secondary Endpoint: OS in 612 Patients, $PFS_{brainmets}$, ORR

a. Trastuzumab administered as a subcutaneous dose (600 mg q1wkx3) was allowed; trastuzumab biosimilar (intravenous or subcutaneous formulations) was allowed if determined appropriate by the investigator and approved for use by national regulatory authorities.

Murthy RK, et al. N Engl J Med 2020;382:597-609

https://clinicaltrials.gov/ct2/show/NCT02614794

Overall Survival in the total study population[a]



	Events	HR (95% CI)	P Value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

Δ5,5 months

Median overall study follow-up: 29.6 months

a) Per protocol prespecified subgroup analysis after ~ 2 years from the last randomization; crossover to the tucatinib arm from placebo was permitted (first patient crossover 02/2020); data cut-off 8th of February 2021.

Curigliano G et al final overall survival analysis. Ann Oncol. 2022 Mar;33(3)321-329

ESMO DEEP DIVE:
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EVIDENCE FOR TUCATINIB AFTER TRASTUZUMAB DERUXTECAN?

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REAL-WORLD-EVIDENCE (RWE): TUCATIINIB AFTER T-DXD
(FLATIRON[1], KOMODO[2], MAREKTSCAN[3], UNICANCER[4])

- RWE database data on tucatinib in routine use (950+ patients)[1,2,3,4]
- Flatiron, Komodo & MarketScan:
- Previous therapy situation (median 2 previous therapies each); high proportion of brain metastases (70-76%)[1,2,3]
- Unicancer: Later therapy situation (median of 4 previous therapies); lower proportion of brain metastases (39%)4
- With prior therapy, the efficacy parameters of the Unicancer cohort are numerically slightly lower than H2C; Flatiron, Komodo & MarektScan are comparable to HER2Climb in a similar pre-treatment situation[1,2,3,4]
- The results underscore long-term efficacy of tucatinib in HER2+ MBC[1]
- **With tucatinib-based therapy, relevant efficacy was observed in all 4 studies after T-DXd (4th-5th line) [33% response rate; mOS up to 13.4 months]**[1,2,3,4]

H2C, HER2CLIMB-Studie; HER2, Human Epidermal Growth Factor Receptor 2; MBC, metastasiertes Mammakarzinom; mOS, medianes Gesamtüberleben; RWE, Real World Evidence

1 - Kaufmann PA et al. Frontiers Oncology 2023, 13:1264861; 2 - Anders C et al. ASCO2023: Abstract 1051 und Poster; 3 - Anders C et al. AMCP 2023: Abstract C9 und Poster; 4 - Frenel J-S. et al. JAMA Netw Open. 2024;7(4):e244435

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FURTHER LINES OF TREATMENT: MANY OPTIONS

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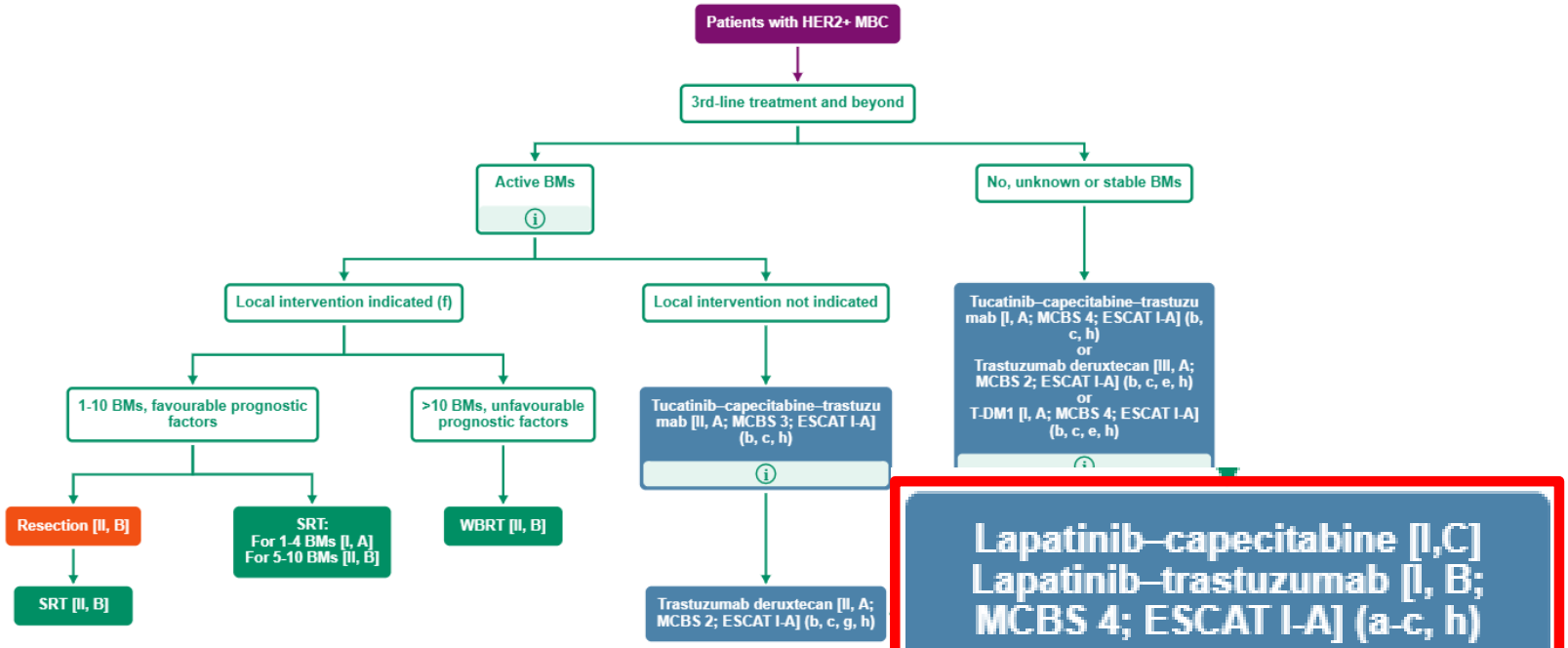
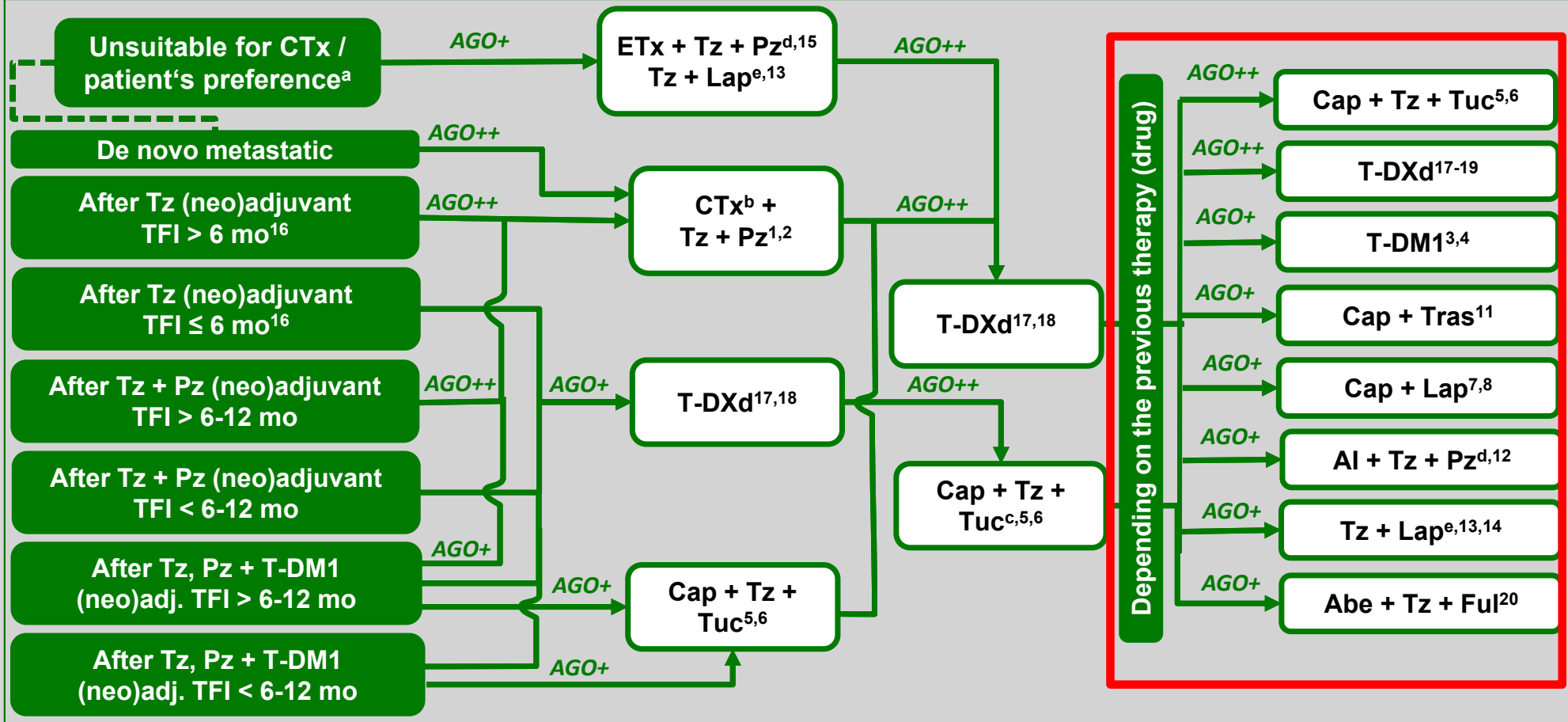
What to do after three or more lines?



HER2-positive Metastatic Breast Cancer: 1st-3rd-line



Abe, Abemaciclib; AI, aromatase inhibitor; Cap, capecitabine; CTx, chemotherapy; ETx, endocrine therapy; Ful, Fulvestrant; HR, hormone receptor; Lap, lapatinib; mo, months; Ner, neratinib; Pz, pertuzumab; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TFI, treatment-free interval; Tuc, tucatinib; Tz, trastuzumab; [a] no overall survival benefit, consider induction chemotherapy; [b] docetaxel (++), paclitaxel (++) or nab-paclitaxel (+); [c] only after T-DM1; [d] only if HR pos; [e] only if HR neg.

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Guidelines Breast
Version 2024.1E

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FORSCHEN
LEHREN
HEILEN

SUMMARY:
FIRST LINE THERAPY DEPENDING ON PRETREATMENT

- Start with taxane / trastuzumab / pertuzumab (also if pretreated with this) if recurrence-free interval is longer than 6-12 month.

- If recurrence free interval is less than 6-12 month, start according to second line therapy

SUMMARY:
SECOND / FURTHER LINE THERAPY DEPENDING ON PRETREATMENT

- Second line therapy depending also on presence of brain metastases
- For most patients trastuzumab deruxtecan as second line therapy and tucatinib / trastuzumab / capecitabine as third line
- Further line options include chemotherapy plus trastuzumab, T-DM1, and maybe also TKIs

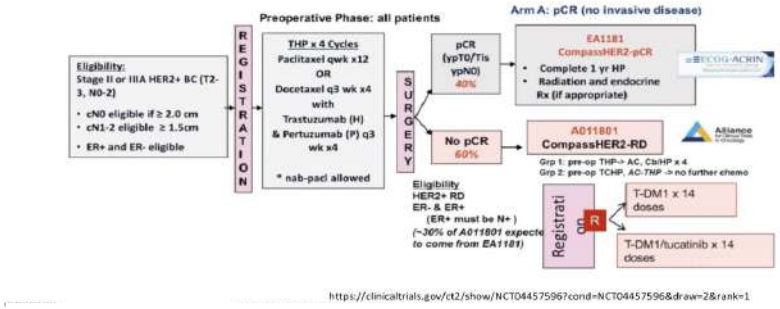
- **Do not forget clinical trials!**

THE TREATMENT LANDSCAPE WILL CHANGE

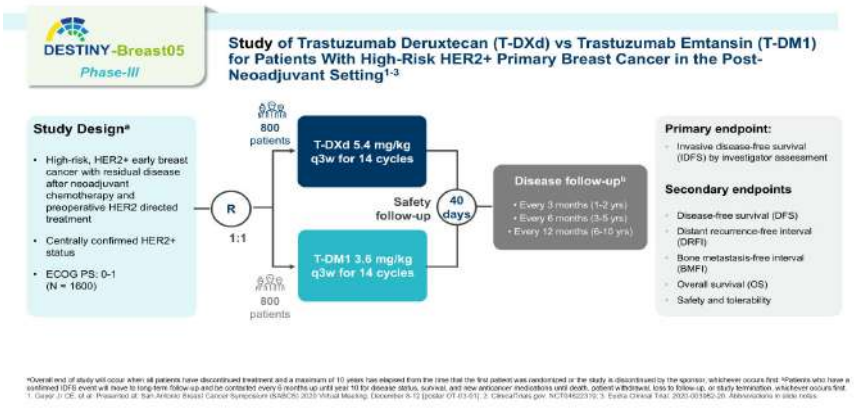
New compunds are also examined in EBC and early lines of treatment in MBC

EBC

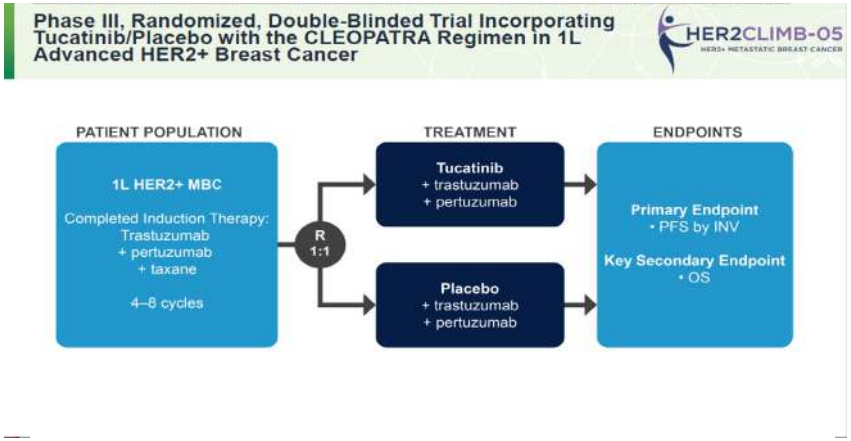
CompassHER2 (NCT04266249; NCT04457596)

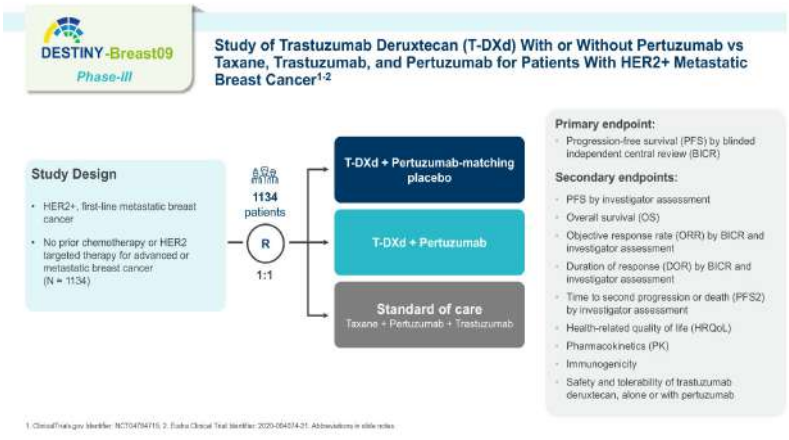


https://clinicaltrials.gov/ct2/show/NCT04457596?cond=NCT04457596&draw=2&rank=1



MBC





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CONCLUSION

Many new options and some open questions in HER2-positive metastatic breast cancer due to a rapidly changing treatment landscape

We need to generate real world evidence and understand better mechanisms of resistance to optimize sequencing of therapy

THANK YOU

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BREAST CANCER

HER2+ METASTATIC BREAST CANCER

Do we need to think about other targets as well?

Giuseppe Curigliano MD PhD

European Institute of Oncology, IRCCS

University of Milano, Milano, Italy

ESMO WEBINAR SERIES

DECLARATION OF INTERESTS

Giuseppe Curigliano

- Board Member: Ellipses
- Consultant: Lilly, Novartis, Seagen, Roche-Genentech, Pfizer, Menarini, Astra Zeneca, Daichii Sankyo, BMS, Celcuity, Blueprint, Gilead
- Research grants to my Institute: MSD, Astra Zeneca
- Speakers bureau: Lilly, Novartis, Seagen, Roche-Genentech, Pfizer, Menarini, Astra Zeneca, Daichii Sankyo, BMS, Celcuity, Blueprint, Gilead
- Stock ownership: None
- Leadership roles: ESMO Open Editor in Chief, ESMO President Elect

OUTLINE

Targeting PD-L1
Targeting ER
Targeting mTOR
Targeting CDK 4-6
Targeting PIK3CA

OUTLINE

Targeting PD-L1

Targeting ER

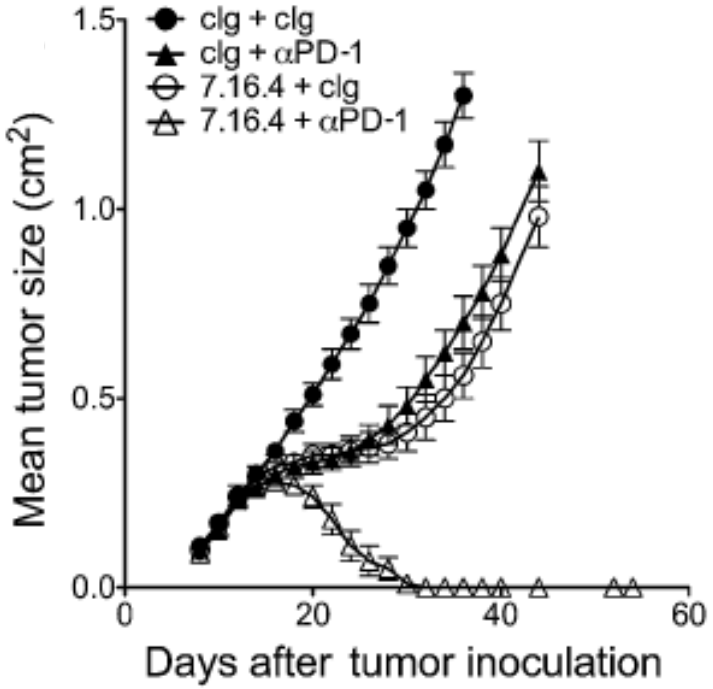
Targeting mTOR

Targeting CDK 4-6

Targeting PIK3CA

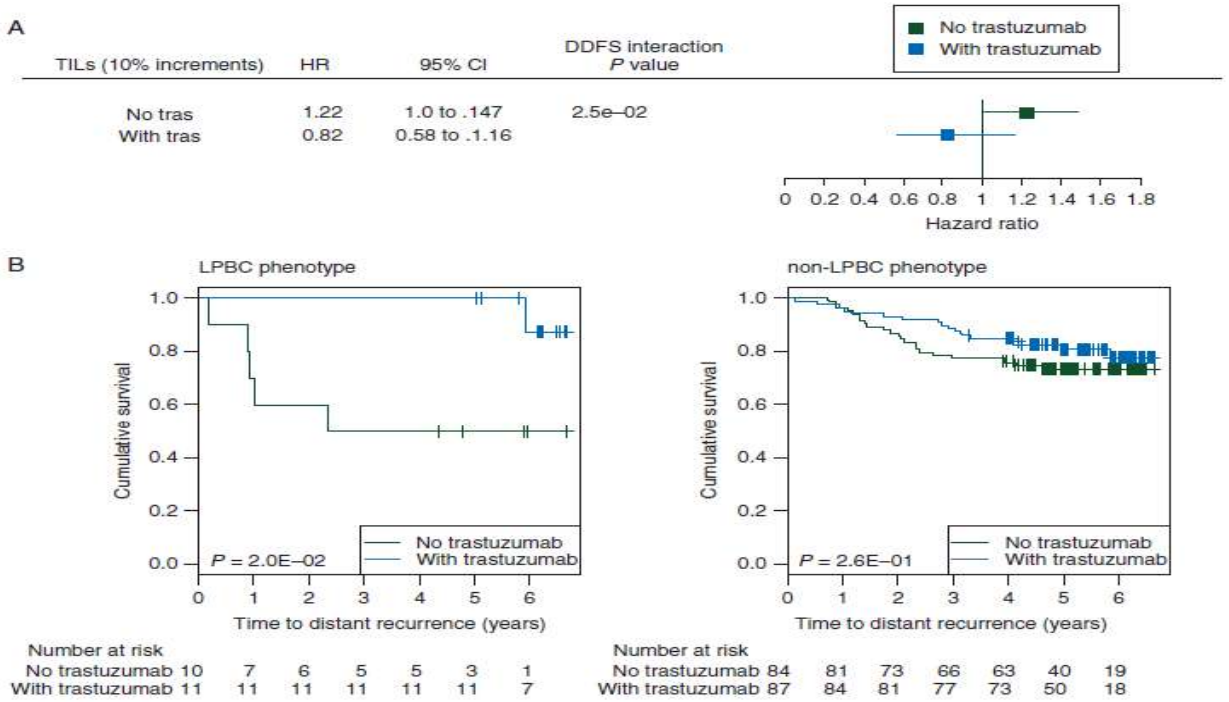
TARGETING PD-L1

- HER2-positive breast cancer has high levels of T cell infiltration
- TILs are associated with improved prognosis and response to trastuzumab and chemotherapy[1,2]
- Trastuzumab has been shown to have immune mediated mechanisms of action[3,4]
- Preclinical studies suggest immune-mediated mechanisms of trastuzumab resistance that can be overcome with checkpoint inhibition combinations[5]



[1] Loi et al, J Clin Oncol 2013; [2] Loi et al, Ann Oncol 2014 [3] Clynnes et al Nat Med 2002
[4] Park et al, Cancer Cell 2011; [5] Stagg, Loi et al, PNAS 2011

TARGETING PD-L1



FinHER: Loi et al, Annals of Oncology 2014

TARGETING PD-L1
PANACEA TRIAL

Patients
- Centrally confirmed HER2+
- ECOG 0-1
- Tumor biopsy sample <1yr
- Measurable disease RECIST 1.1
- No limit of prior systemic treatment
- Documented PD on trastuzumab or TDM-1

PD-L1 + →

Phase Ib
Pembrolizumab
2mg/kg and 10mg/kg IV +
trastuzumab Q3W

Phase II
Pembrolizumab 200mg IV
+ trastuzumab Q3W

PD-L1 - →

Phase II
Pembrolizumab 200mg IV
+ trastuzumab Q3W

Protocol specified follow-up.
Treatment until progression, toxicity, patient withdrawal, investigator decision, or maximum 2 years

Loi S, et al. Lancet Oncol. 2019 Mar;20(3):371-382.

TARGETING PD-L1

146 patients screened
68 (53.5%) PD-L1 - positive
Feb. 2015- April 2017
11 sites, 5 countries

Ineligible as HER2 negative (10.6%)

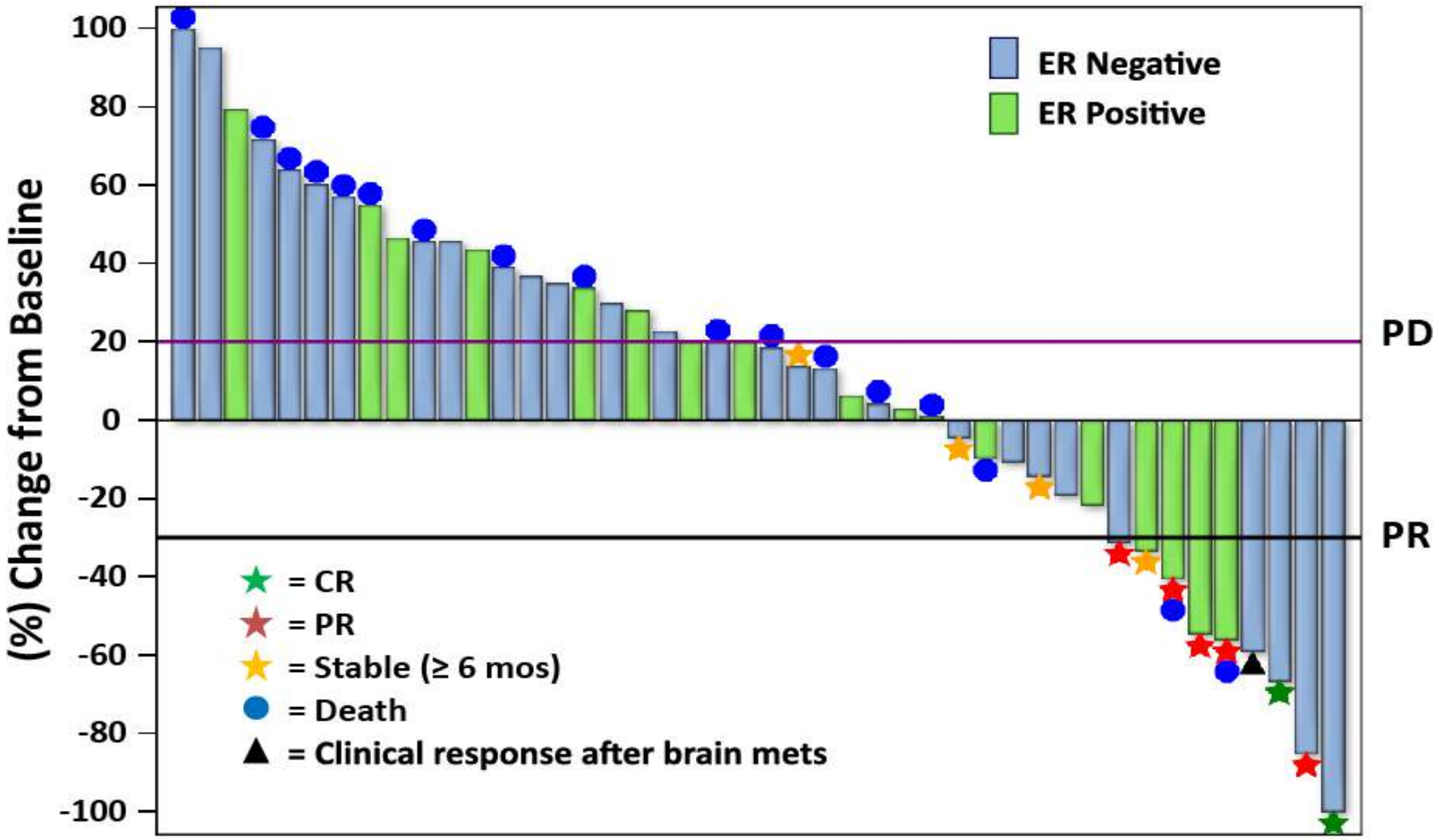
Enrolled 58 (39.7% of screened)

- **6 Phase Ib PD-L1 positive**
- **40 Phase II PD-L1 positive**
  - **41% ER pos**
  - **59% ER neg**
- **12 PD-L1 negative**
  - **50% ER pos**
  - **50% ER neg**

- **On treatment: 3 (5%)**
- **Discontinued**
  - **PD: 46 (84%)**
  - **Death from PD: 1 (2%)**
  - **AE: 6 (10%)**
  - **Withdrew consent: 1 (2%)**
  - **Patient deterioration: 1 (2%)**

Loi S, et al. Lancet Oncol. 2019 Mar;20(3):371-382.

TARGETING PD-L1



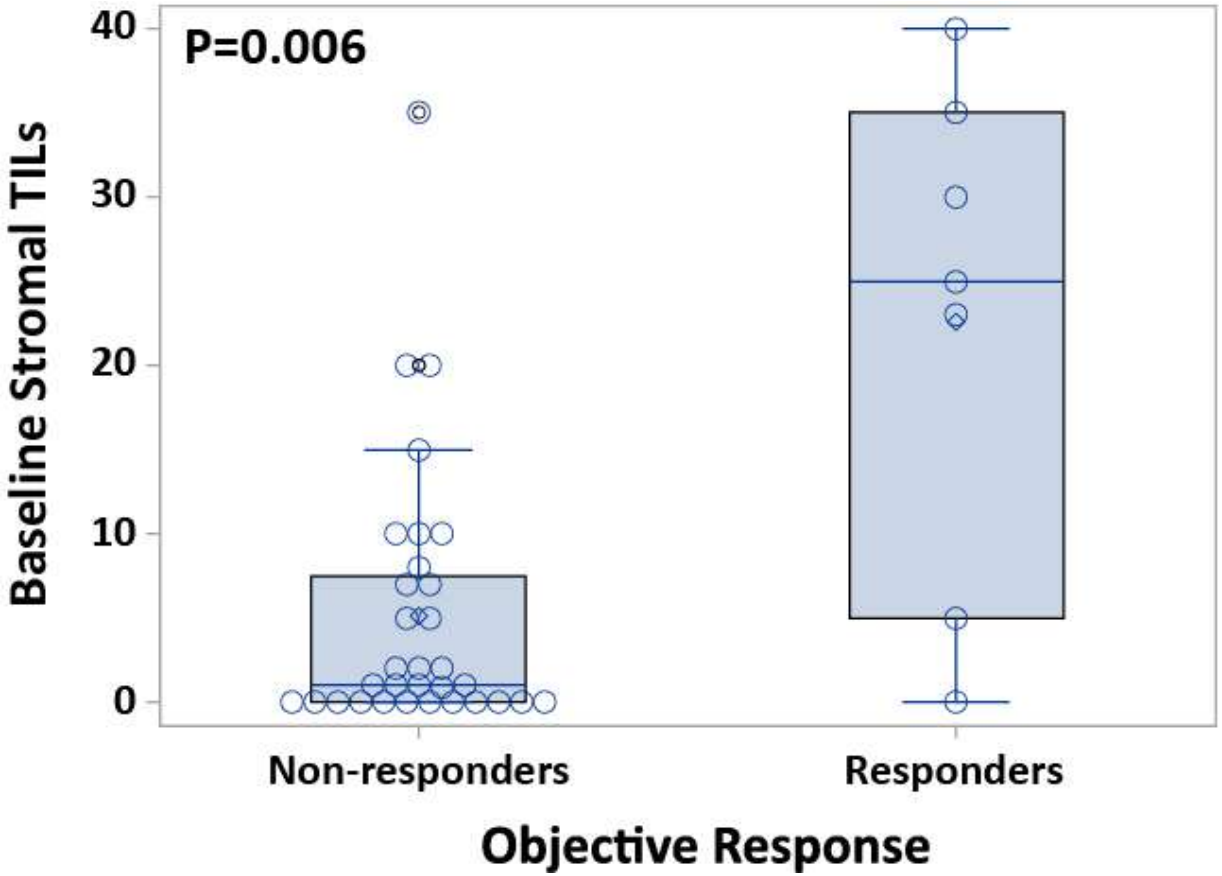
N=44 as excludes 2 patients without follow-up measurements of target lesions

▲ brain met not detected at screening in a patient with PR

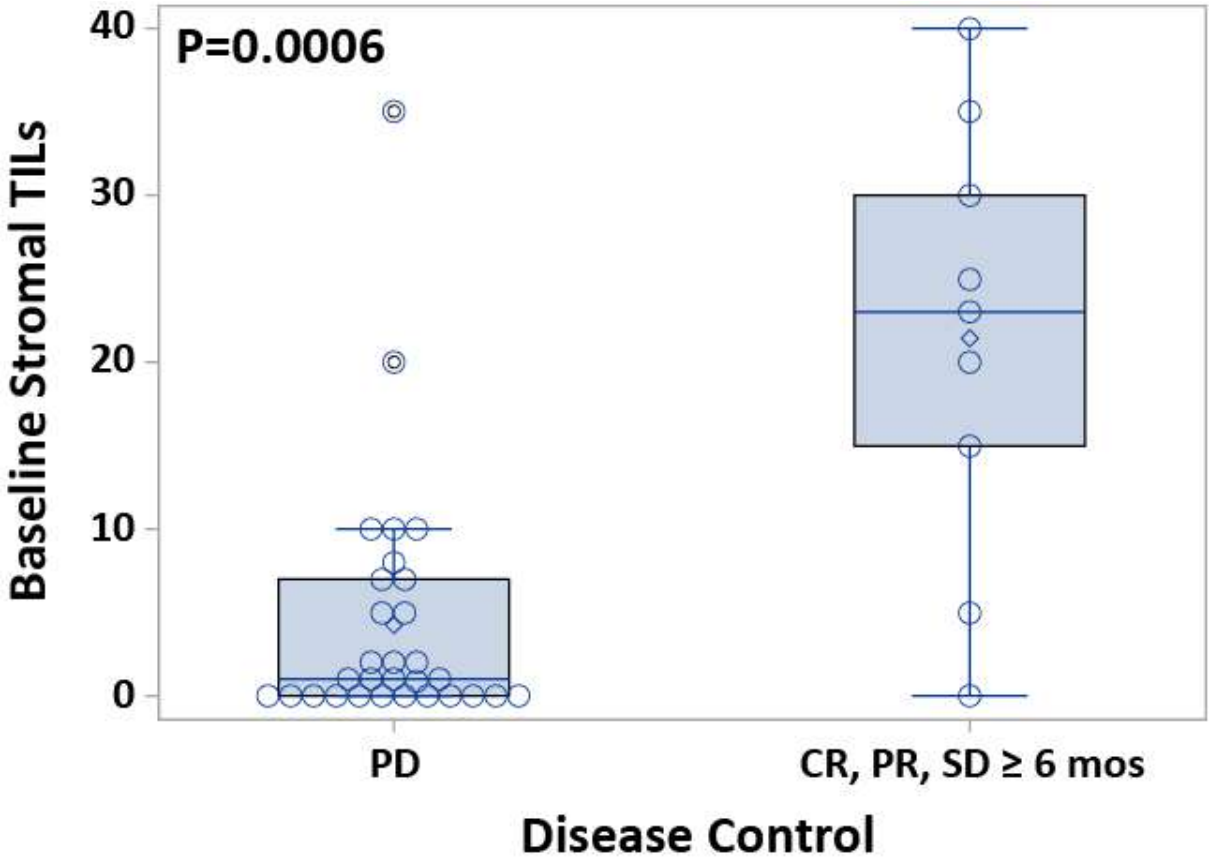
Loi S, et al. Lancet Oncol. 2019 Mar;20(3):371-382.

TARGETING PD-L1

- *Baseline sTILs and ORR*

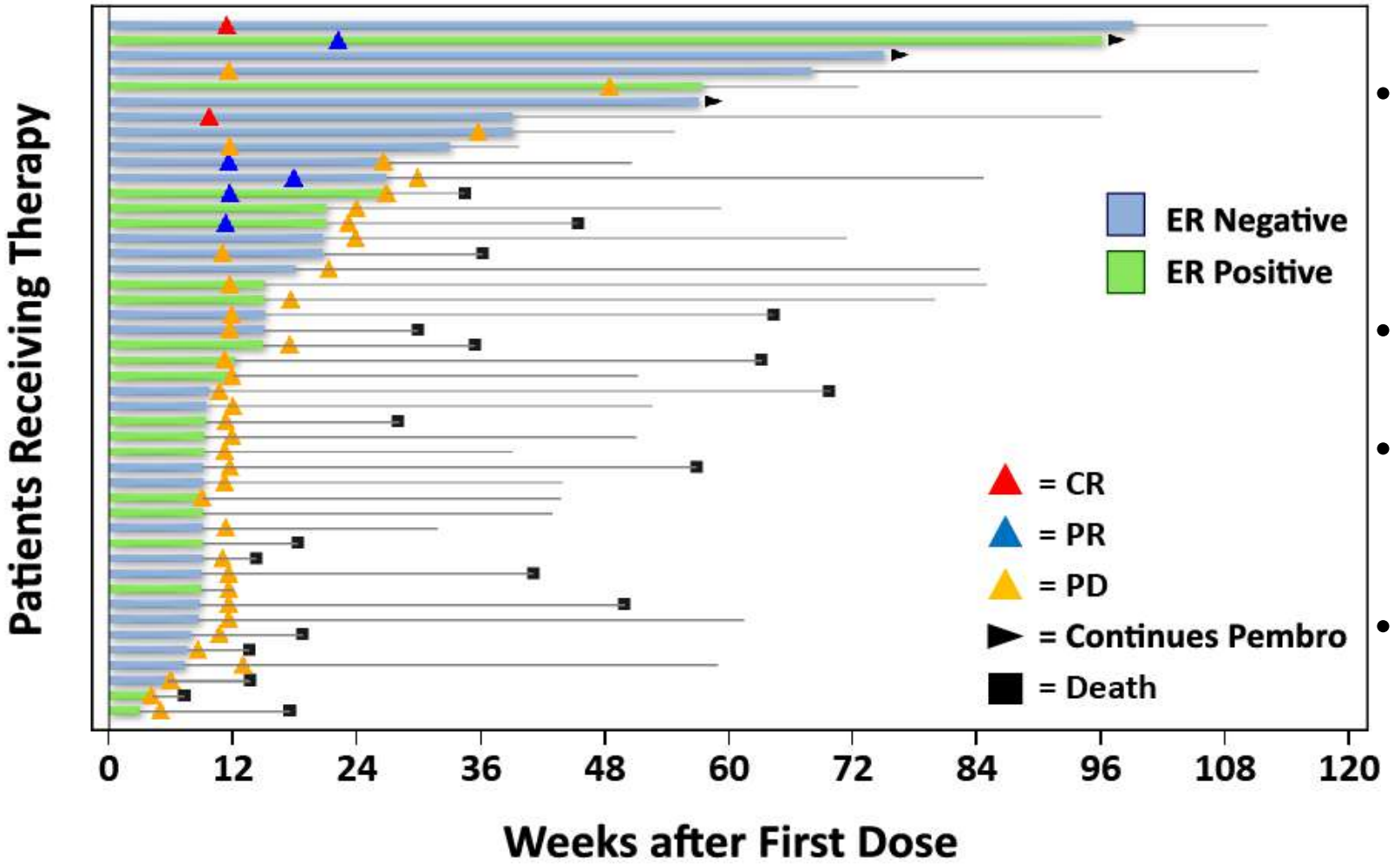


- *Baseline sTILs and DCR*



Loi S, et al. Lancet Oncol. 2019 Mar;20(3):371-382.

TARGETING PD-L1



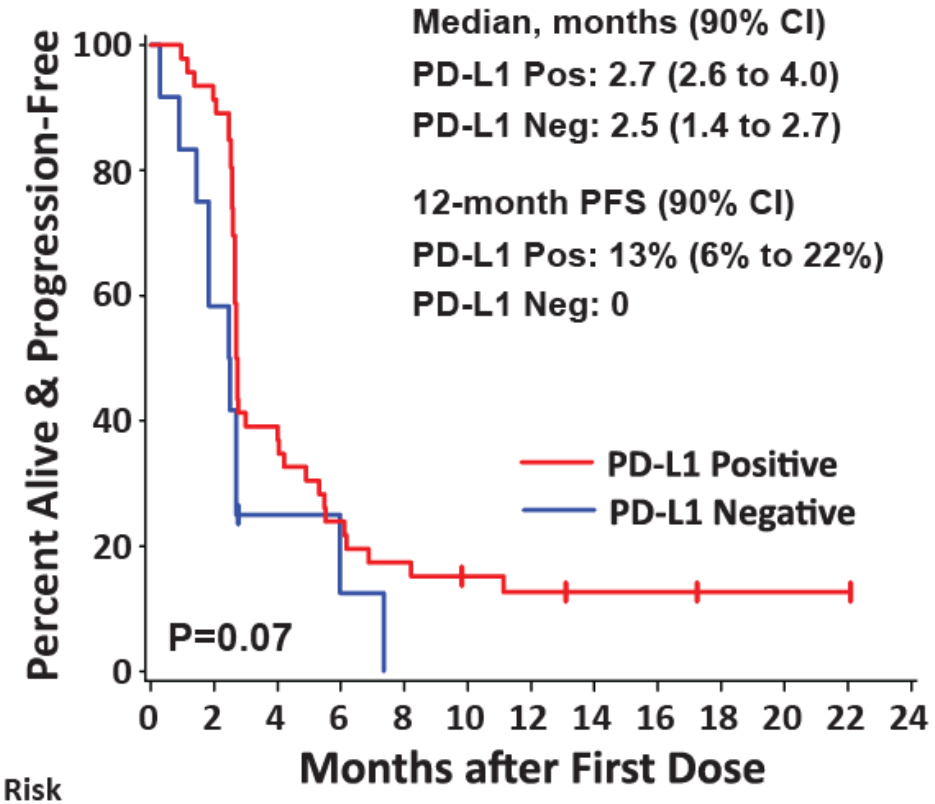
- **Median duration of disease control[1]: 11.1 months (90% CI: 6.2 -∞)**
- **Median DoR[2]: 3.5 months (90% CI: 2.7 - ∞)**
- **Mean DoR[2]: 10 months (90% CI: 2.7-23.1)**
- **Five patients (10.8%) continue with no progression at time of reporting**

Loi S, et al. Lancet Oncol. 2019 Mar;20(3):371-382.

[1]DCR: CR, PR, or SD ≥ 6 months, [2] timing from first restaging at 12 weeks

TARGETING PD-L1

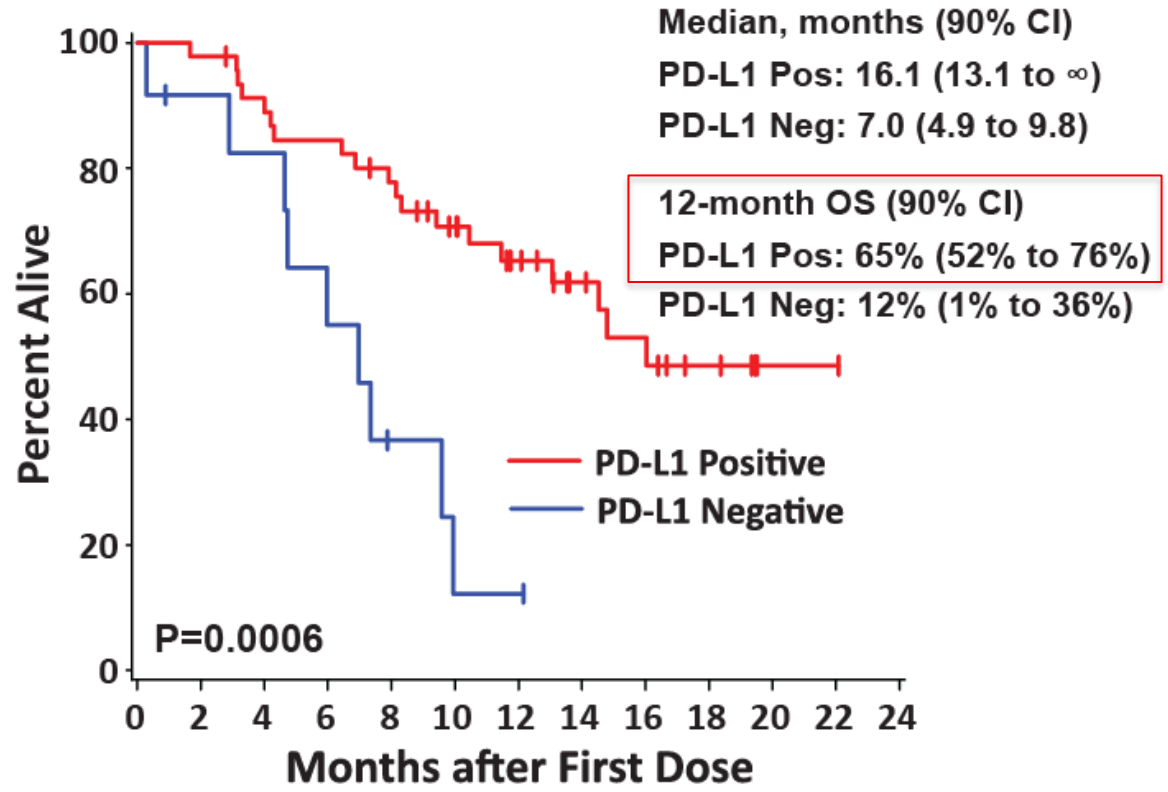
PFS



Number at Risk

PD-L1 Positive	46	18	8	5	4	3	2
PD-L1 Negative	12	2	0	0	0	0	0

OS

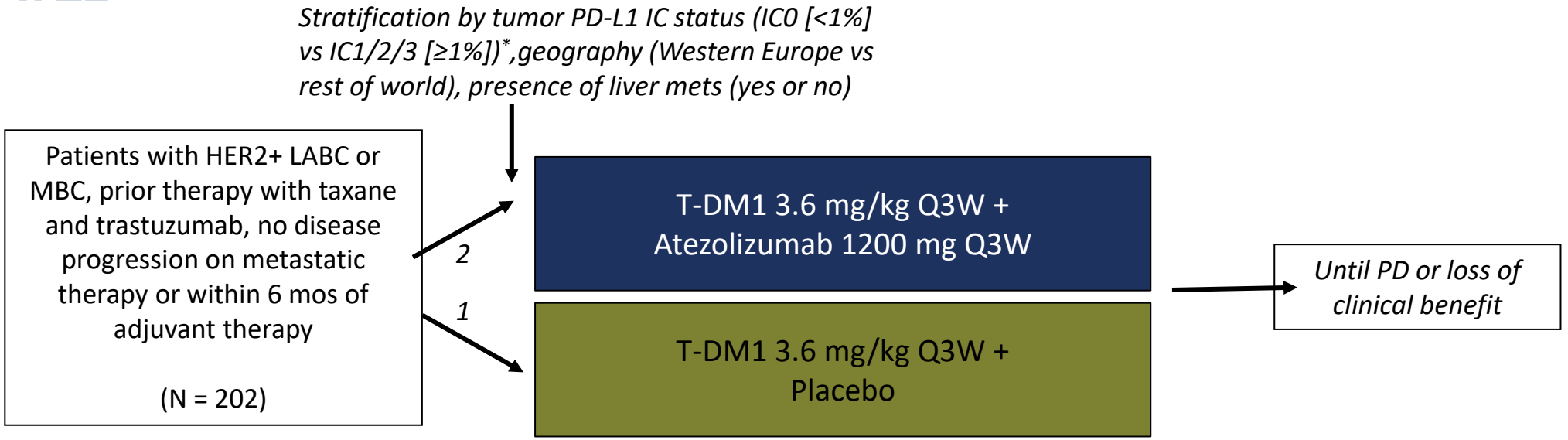


	46	41	34	21	12	4	3
	12	9	3	1	0	0	0

Loi S, et al. Lancet Oncol. 2019 Mar;20(3):371-382.

TARGETING PD-L1

KATE2



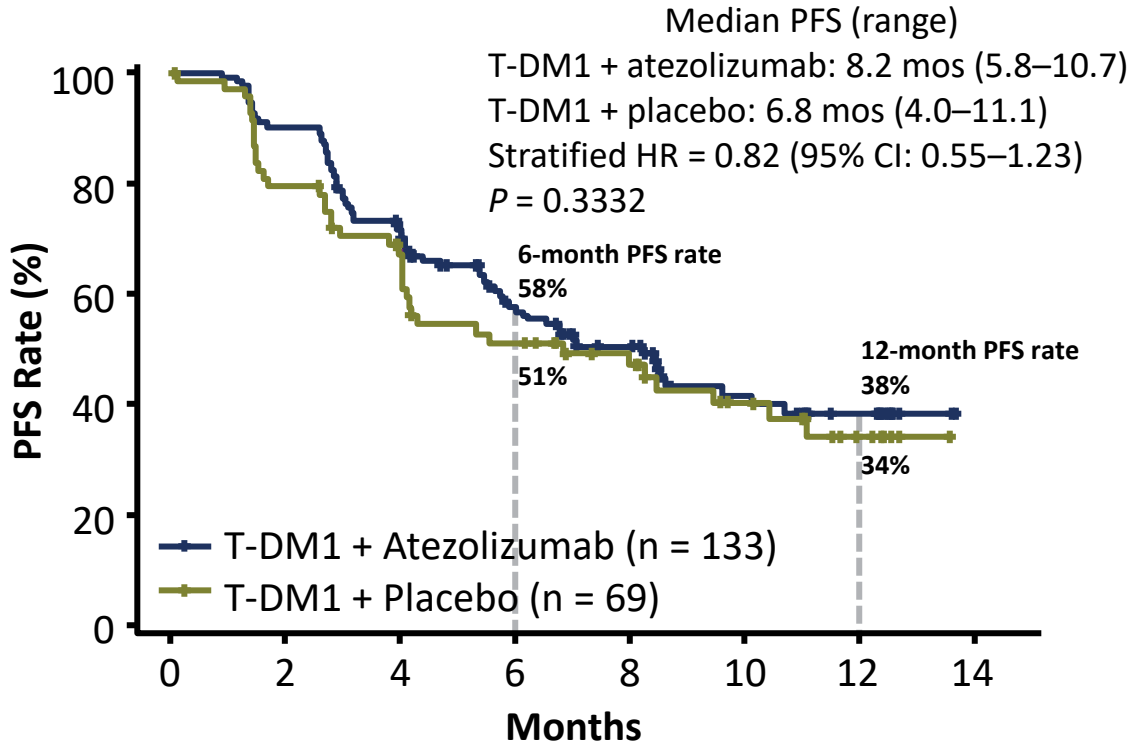
- Primary endpoint: PFS by investigator
- Secondary endpoints: OS, ORR, DOR

- Exploratory endpoints: PFS in PD-L1+ disease, Biomarker subgroups (PD-L1, *PIK3CA* mutation status, HER2 expression, TILs, CD8 expression)

Emens LA, et al. Lancet Oncol. 2020 Oct;21(10):1283-1295. doi: 10.1016/S1470-2045(20)30465-4. PMID: 33002436.

TARGETING PD-L1
KATE2: PFS IN ITT AND PD-L1 IC+ POPULATIONS

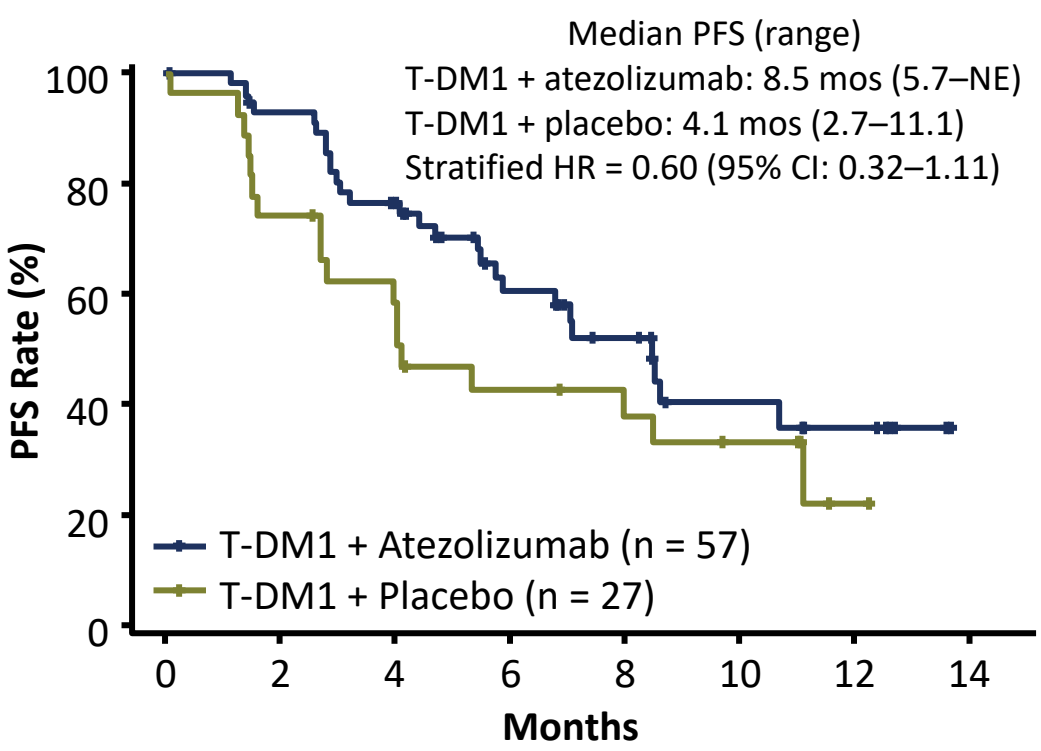
ITT



No. of Patients at Risk

T-DM1 + Atezolizumab	133	131	118	100	90	74	59	46	42	26	25	21	15	3
T-DM1 + Placebo	69	66	54	46	42	33	31	25	23	18	15	14	7	1

PD-L1 IC+

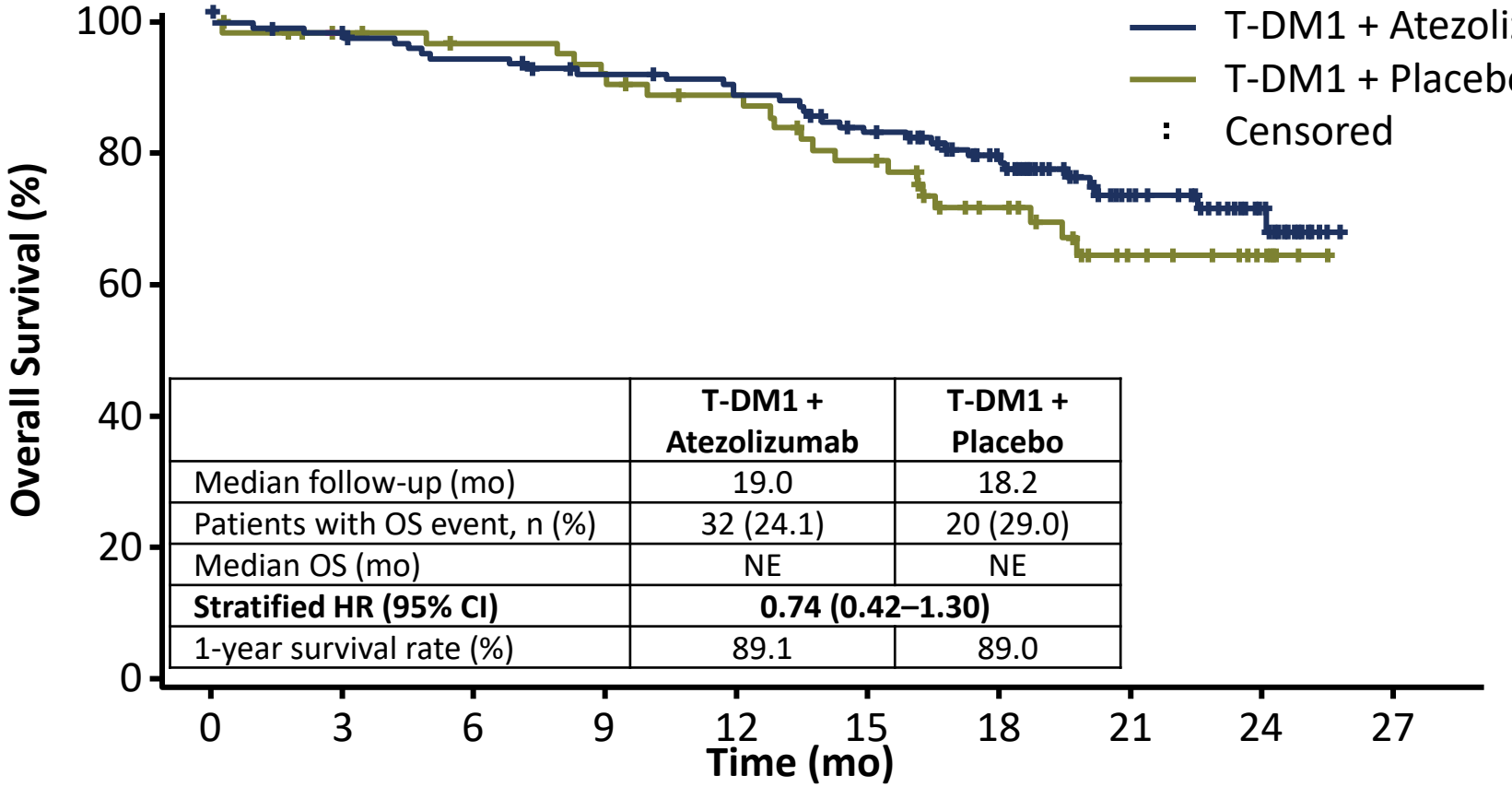


No. of Patients at Risk

T-DM1 + Atezolizumab	57	56	51	44	40	31	24	19	16	9	9	8	6	2
T-DM1 + Placebo	27	26	20	16	15	11	10	9	8	7	6	6	1	

Emens LA, et al. Lancet Oncol. 2020 Oct;21(10):1283-1295. doi: 10.1016/S1470-2045(20)30465-4. PMID: 33002436.

TARGETING PD-L1



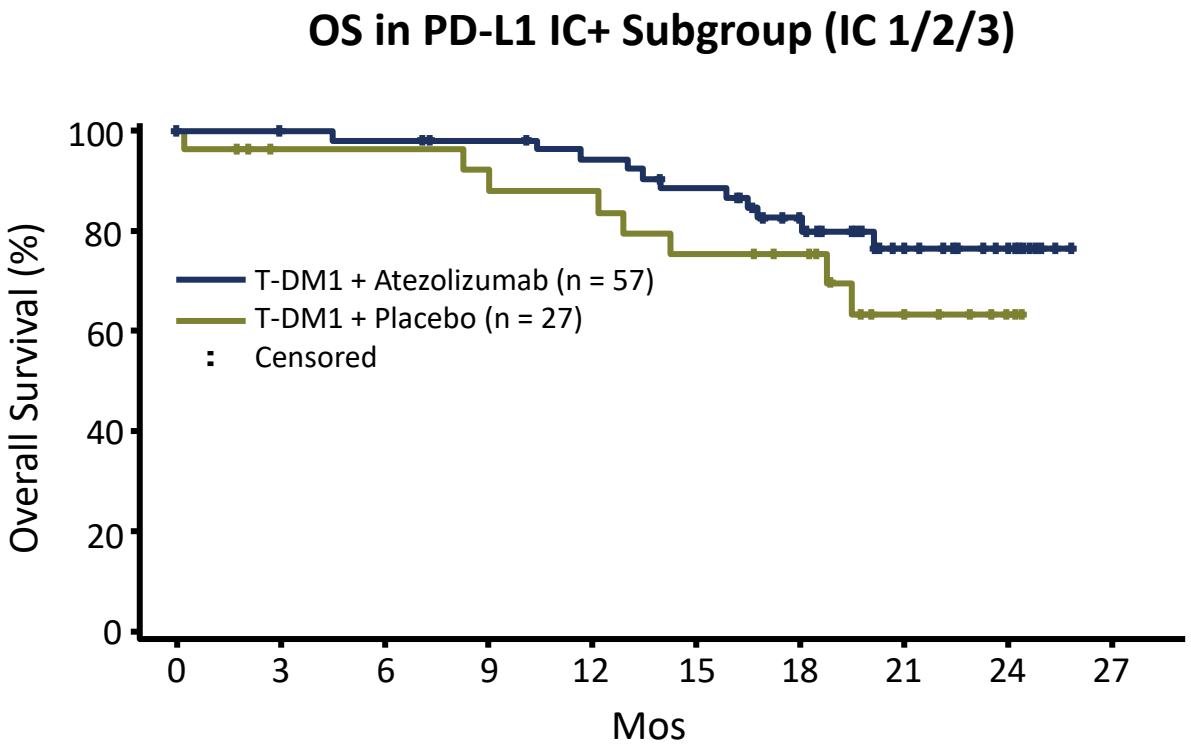
	T-DM1 + Atezolizumab	T-DM1 + Placebo
Median follow-up (mo)	19.0	18.2
Patients with OS event, n (%)	32 (24.1)	20 (29.0)
Median OS (mo)	NE	NE
Stratified HR (95% CI)	**0.74 (0.42–1.30)**	
1-year survival rate (%)	89.1	89.0

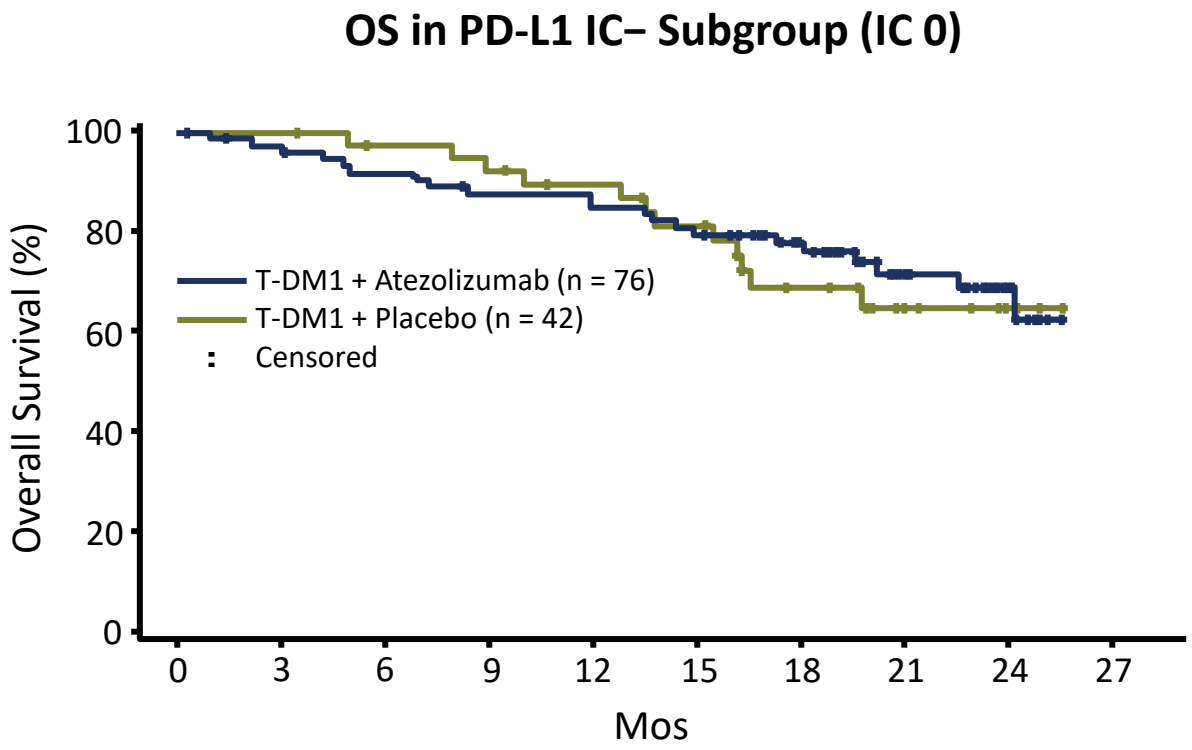
No. of Patients at Risk

T-DM1 + Atezolizumab	133	131	130	129	126	122	122	121	118	116	116	114	111	111	110	104	101	98	86	78	66	56	44	42	34	21	6
T-DM1 + Placebo	69	67	66	64	63	62	61	61	60	58	55	54	54	51	48	47	45	37	35	29	23	16	14	12	8	1	

Emens LA, et al. Lancet Oncol. 2020 Oct;21(10):1283-1295. doi: 10.1016/S1470-2045(20)30465-4. PMID: 33002436.

TARGETING PD-L1





- One-year OS rate was numerically higher with the addition of atezolizumab in PD-L1 IC+ subgroup

Emens LA, et al. Lancet Oncol. 2020 Oct;21(10):1283-1295. doi: 10.1016/S1470-2045(20)30465-4. PMID: 33002436.

TARGETING PD-L1

KATE3

A Phase III study of T-DM1 in combination with atezolizumab or placebo in patients with previously treated HER2-positive and PD-L1–positive locally advanced or metastatic breast cancer

Eligibility criteria

- HER2+, PD-L1+ LABC or mBC
- Prior trastuzumab (± pertuzumab) and taxane-based therapy
- Progression during most recent mBC treatment or during, or within 6 months after completing, neoadjuvant and/or adjuvant therapy
- N=350

R
1:1

Atezolizumab 1200 mg q3w + T-DM1 3.6 mg/kg q3w

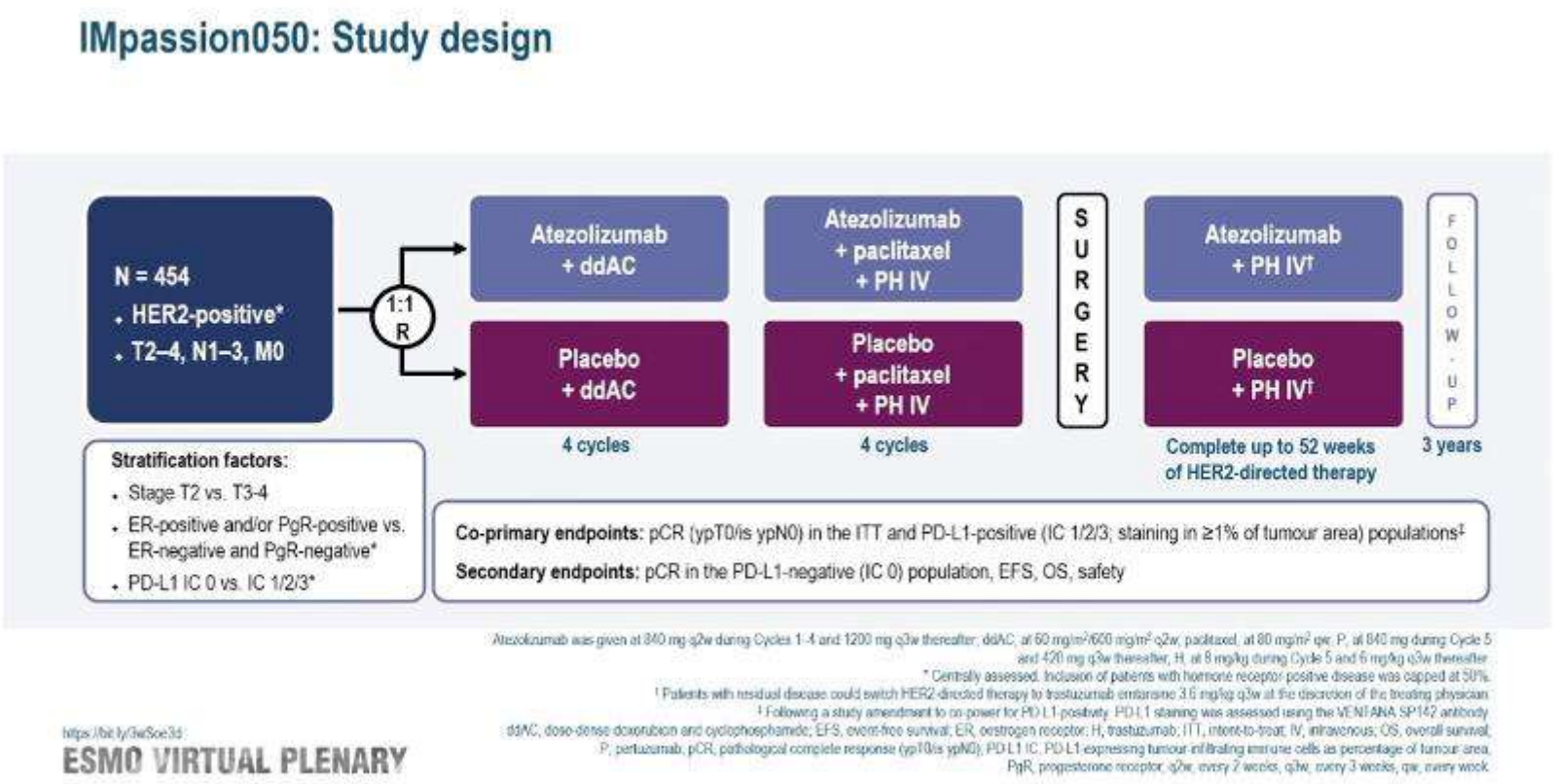
Placebo + T-DM1 3.6 mg/kg q3w

Study endpoints

Primary endpoint
- PFS
- OS

Secondary endpoints
- ORR
- DoR
- PFS and OS in patients with BM

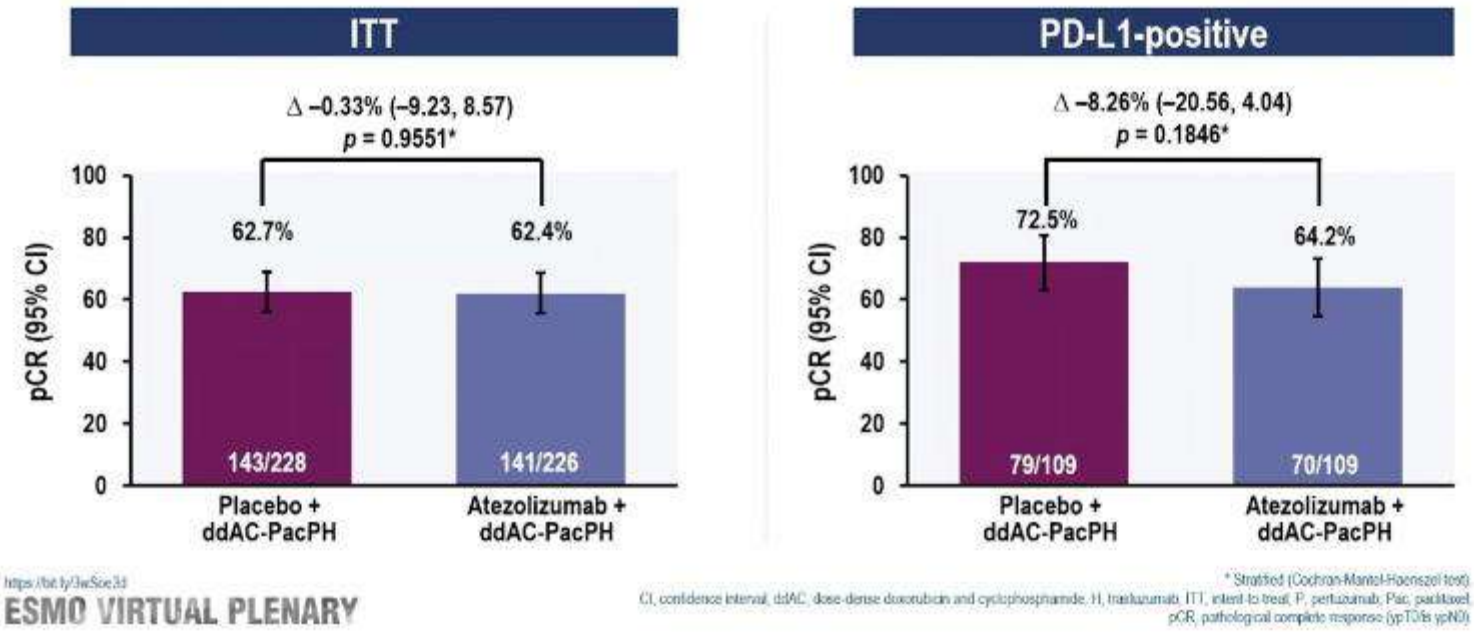
TARGETING PD-L1
IMPASSION 050



Huober J, et al. J Clin Oncol. 2022 Sep 1;40(25):2946-2956.

TARGETING PD-L1

IMpassion050: Co-primary endpoints – pCR in the ITT and PD-L1-positive populations



https://bit.ly/3wSce3d

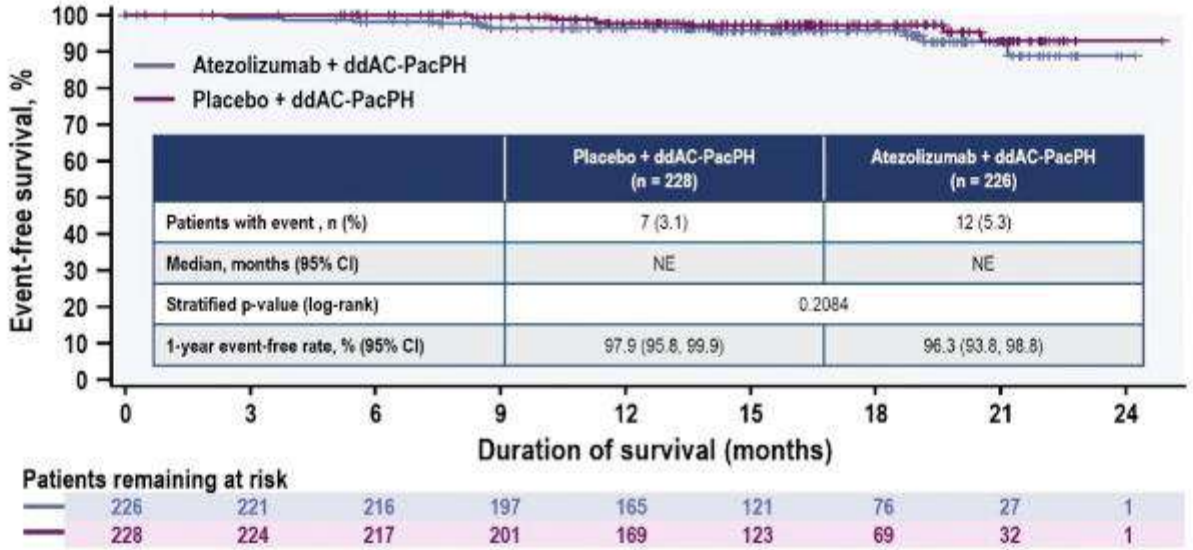
ESMO VIRTUAL PLENARY

* Stratified (Cochran-Mantel-Haenszel test).
CI, confidence interval; ddAC, dose-dense doxorubicin and cyclophosphamide; H, trastuzumab; ITT, intent-to-treat; P, pertuzumab; Pac, paclitaxel; pCR, pathological complete response (ypT0/is ypN0).

Huober J, et al. J Clin Oncol. 2022 Sep 1;40(25):2946-2956.

TARGETING PD-L1

IMpassion050: Secondary endpoint – event-free survival in the ITT population



	Placebo + ddAC-PacPH (n = 228)	Atezolizumab + ddAC-PacPH (n = 226)
Patients with event , n (%)	7 (3.1)	12 (5.3)
Median, months (95% CI)	NE	NE
Stratified p-value (log-rank)	0.2084	
1-year event-free rate, % (95% CI)	97.9 (95.8, 99.9)	96.3 (93.8, 98.8)

https://bit.ly/3wSce3t

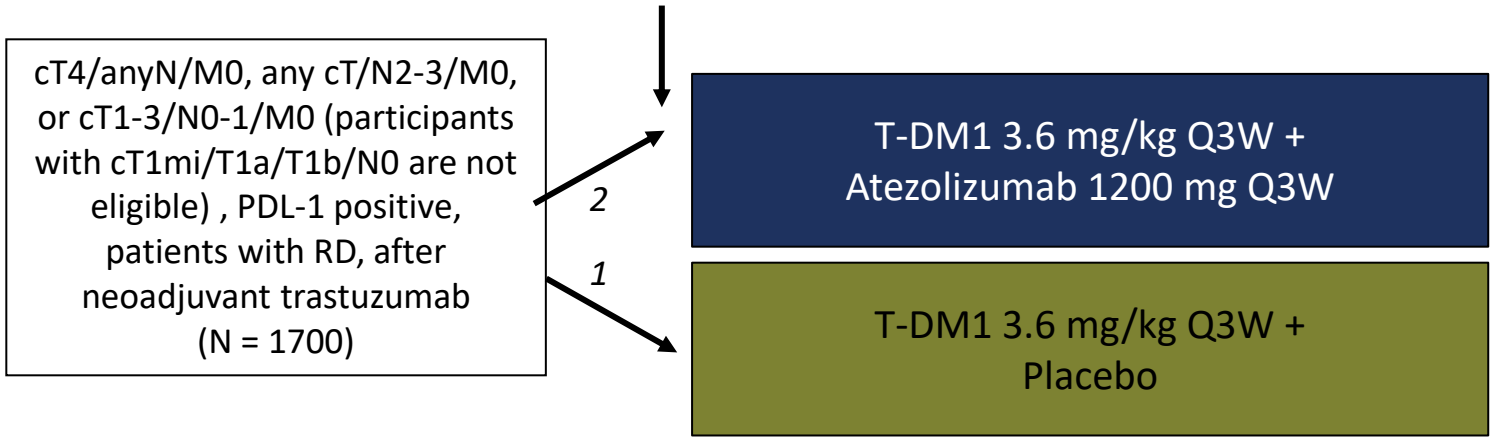
ESMO VIRTUAL PLENARY

CI, confidence interval; ddAC, dose-dense doxorubicin and cyclophosphamide; H, trastuzumab; ITT, intent-to-treat; NE, not evaluable; P, pertuzumab; Pac, paclitaxel

Huober J, et al. J Clin Oncol. 2022 Sep 1;40(25):2946-2956.

TARGETING PD-L1

ASTEFANIA



- Primary endpoint: IDFS

- Exploratory endpoints: Biomarker subgroups (PD-L1, *PIK3CA* mutation status, HER2 expression, TILs, CD8 expression)

OUTLINE

Targeting PD-L1

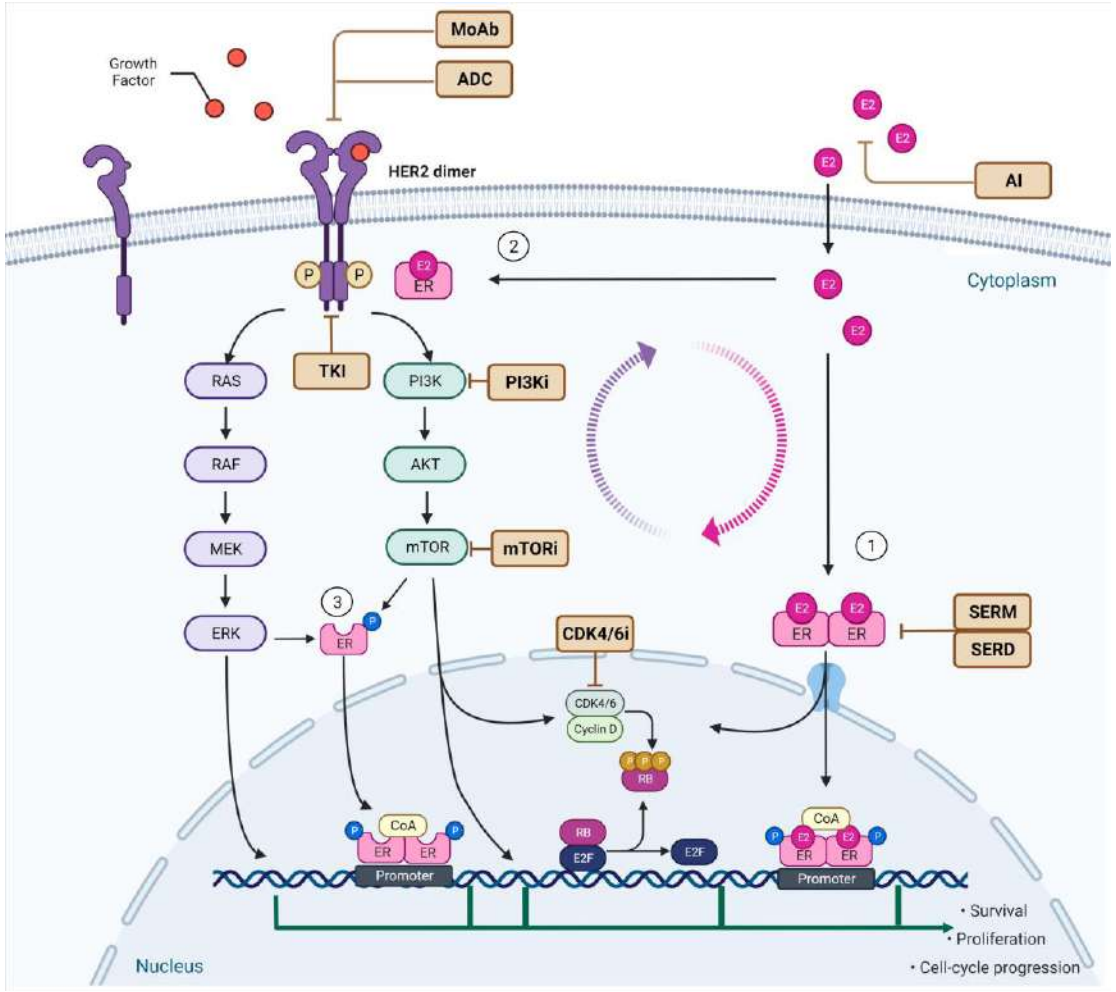
Targeting ER

Targeting mTOR

Targeting CDK 4-6

Targeting PIK3CA

TARGETING ER PATHWAY



Boscolo Bielo L, et al. Cancer Treat Rev. 2024 Jul;128:102761. doi: 10.1016/j.ctrv.2024.102761.

TARGETING ER PATHWAY

Trial	Phase	No of patients	Study Population	Treatment arms	Primary Endpoint	Results (95% CI)	Secondary endpoint (95% CI)
TAnDEM (NCT00022672)	III	207	1-2L HER2+/HR+ mBC	A: Anastrozole + Trastuzumab B: Anastrozole + placebo	PFS	A: 4.8 months (3.7 - 7.09) B: 2.4 months (2.0 to 4.6) Hazard ratio 0.63 (0.47-0.84; p = 0.006)	OS A: 28.5 months (22.8 -42.4; p=0.325) B: 23.9 months (18.2 - 37.4)
eLEcTRA (NCT00171847)	III	93	1L HER2+/HR+ mBC	A: Letrozole + Trastuzumab B: Letrozole + Placebo	TTP	A: 14.1 months B: 3.3 months Hazard ratio 0.67 (0.35-1.29; p = 0.23)	OS Not statistically significant (data not reported)
EGF30008 (NCT00073528)	III	219	1L HER2+/HR+ mBC	A: Letrozole + Lapatinib B: Letrozole + placebo	PFS	A: 8.2 months B: 3.0 months Hazard ratio 0.71 (0.53-0.96; p=0.019)	OS Hazard ratio 0.77 (0.52, 1.14), p=0.185
PERTAIN (NCT01491737)	II	258	1L HER2+/HR+ mBC	A: Trastuzumab + Pertuzumab + Anastrozole B: Trastuzumab + Anastrozole -Optional induction chemotherapy	PFS	A: 20.6 months (14.4 – 28.4) B: 15.8 months (11.0 – 18.7) Hazard ratio 0.67 (0.50–0.89; p= 0.006)	OS A: 60.2 months (47.2 –79.0 months)] B: 57.2 months (45.4 –not reached) Hazard ratio, 1.05 (0.73–1.52; p = 0.783)
ALTERNATIVE (NCT01160211)	III	1286 (219 HR+/HER2+)	≥2L Metastatic HR+ BC	A: AI + Trastuzumab + Lapatinib B: AI + Trastuzumab C: AI + Lapatinib	PFS	A: 11 months (8.3 - 13.8) B: 5.7 months (5.5 - 8.4) C: 8.3 months (5.8 - 11.2)	OS A: 46 months(46.0-NE) B: 40 months (23.0-NE) C: 45.1 months (22.3-NE)
SYSUCC-002 (NCT01112826)	III	392	1L HER2+/HR+ mBC	A: ET + Trastuzumab B: chemotherapy (Capecitabine , Vinorelbine, or Gemcitabine) + Trastuzumab	PFS	A: 19.2 months (16.7 – 21.7); B: 14.8 months (12.8 –16.8) Hazard ratio 0.88 (0.71 – 1.09; p < 0.0001)	NA

Arpino et al. Clinical Cancer Research. Published online January 30, 2023; Hua X et al. Clinical Cancer Research. 2022;28(4):637-645.

TARGETING ER PATHWAY

herdERA

Eligibility criteria

- HER2-positive LA or mBC
- Maintenance phase: Complete a minimum of 4 cycles of induction therapy, achieve a minimum of stable disease
- ECOG 0–1
- Previously untreated HER2-positive ER-positive
- N=812

Induction therapy: Phesgo + taxane

R 1:1

Phesgo + giredestrant

Phesgo

Study endpoints

Primary endpoint
- PFS

Secondary endpoints
- OS
- ORR
- DoR
- CBR
- Safety and HRQoL

Arpino et al. Clinical Cancer Research. Published online January 30, 2023; Hua X et al. Clinical Cancer Research. 2022;28(4):637-645.

OUTLINE

Targeting PD-L1
Targeting ER
Targeting mTOR
Targeting CDK 4-6
Targeting PIK3CA

TARGETING ER/MTOR PATHWAY

Trial	Phase	No of patients	Study Population	Treatment arms	Primary Endpoint	Results (95% CI)	Secondary endpoint (95% CI)
BOLERO 3[42] (NCT01007942)	III	≥2L HER2+ mBC	A: Trastuzumab + Vinorelbine + Everolimus B: Trastuzumab + Vinorelbine + Placebo	317	250	mPFS 7 months vs 5.78 months	0.93 (0.72–1.20); 0.65 (0.48–0.87)
BOLERO 1[43] (NCT00876395)	III	1L HER2+ mBC	A: Everolimus + Paclitaxel + Trastuzumab B: Placebo + Paclitaxel + Trastuzumab	406	311	mPFS (full study population) 14.9 months vs 14.5 months mPFS (HR- subset)** 20.3 months vs 13.1 months	NA; 0.66 (0.48-0.91)

André F, et al Lancet Oncol. 2014;15(6):580-591; Hurvitz et al. Lancet Oncol. 2015;16(7):816-829. doi:10.1016/S1470-2045(15)00051-0

OUTLINE

Targeting PD-L1
Targeting ER
Targeting mTOR
Targeting CDK 4-6
Targeting PIK3CA

TARGETING CDK 4-6 PATHWAY

Trial	Phase	No of patients	Study Population	Treatment arms	Primary Endpoint	Results (95% CI)	Secondary endpoint (95% CI)
monarcHER (NCT02675231)	II	237	≥3L HER2+/HR+ mBC	A: Abemaciclib + Trastuzumab + Fulvestrant B: Abemaciclib + Trastuzumab C: Trastuzumab + SoC chemotherapy	PFS	A: 8.3 months (5.9–12.6) B: 5.7 months (4.2–7.2) C: 5.7 months (5.4–7.0) A vs. C Hazard ratio 0.67 (0.45 – 1.00; p=0.051)	OS NA
PATRICIA (NCT02448420)	II	71 (cohort B1 28, cohort B2 28)	≥2L mBC Cohort A: HER2+/HR- mBC; Cohort B1 and B2: HER2+/HR+ mBC	B1: Palbociclib + Trastuzumab; B2: Palbociclib + Trastuzumab + Letrozole	6-month PFS	A: 33% B1: 42.8% B2: 46.4%	Biomarkers as predictors of response PAM50 luminal vs non-luminal 10.6 vs. 4.2 months median PFS (Hazard ratio 0.40; p= 0.003)[51]
LORDSHIPS (NCT03772353)	I-II	79	1L HER2+/HR+ mBC	Dalpiciclib + Pyrotinib + Letrozole	AE; ORR	G3-4 AEs 80%; ORR 66.7% (38.4 - 88.2%)	NA

Tolaney et al , Lancet Oncol. 2020;21(6):763-775

TARGETING CDK 4-6 PATHWAY

Patients with early and locally advanced **HER2+ and ER+** (>10%) BC;* chemo-naïve

*HER2, ER, PR and Ki67 centrally confirmed

Herceptin + Pertuzumab + Palbociclib + Fulvestrant

H = Herceptin/trastuzumab, 8 mg/kg on first dose, 6 mg/kg thereafter x 6;
P = Pertuzumab, 840 mg on first dose, 420 mg thereafter x 6;
Palbociclib 125 mg orally QD. x 21 q. 4 wks. x 5
Fulvestrant will be given intra-muscle at the dose of 500 mg every 4 weeks x 5 with an additional 500 mg dose given two weeks after the initial dose

The total duration of neoadjuvant palbociclib (5 cycles every 4 weeks) and fulvestrant (5 administrations every 4 weeks plus the additional dose given two weeks after the initial dose) was selected to match as closely as possible the total duration of the six planned 3-weekly administrations of trastuzumab and pertuzumab

Primary endpoints

- Ki67 changes from baseline before therapy, at 2 weeks, and at surgery
- Change in apoptosis from baseline before therapy and at surgery

Secondary endpoints

- pCR
- ORR
- Tolerability

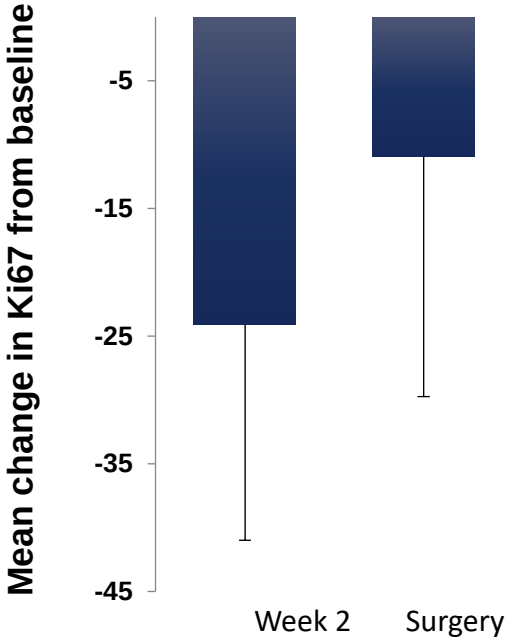
ORR, objective response rate; pCR, pathological complete response defined as absence of invasive cells in breast and axilla (ypT0-ypTis ypN0) at surgery

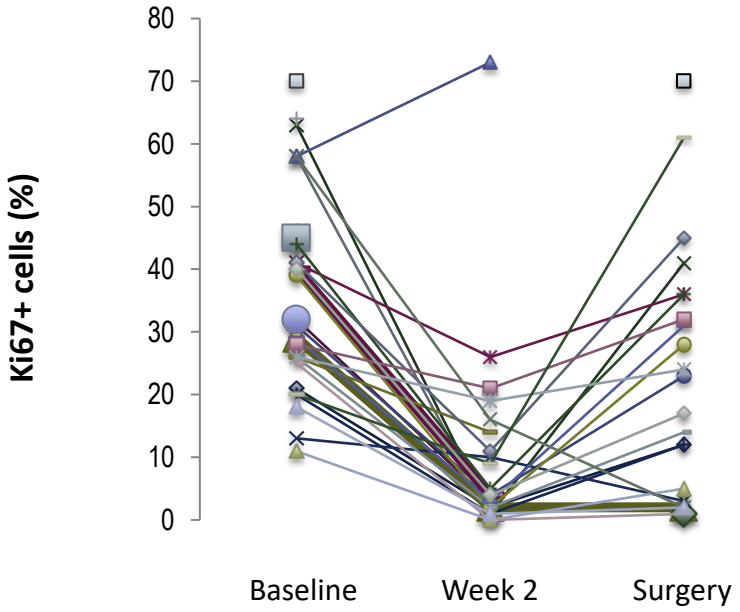
Gianni L, et al. Lancet Oncol 2018

TARGETING CDK 4-6 PATHWAY

Ki67 change

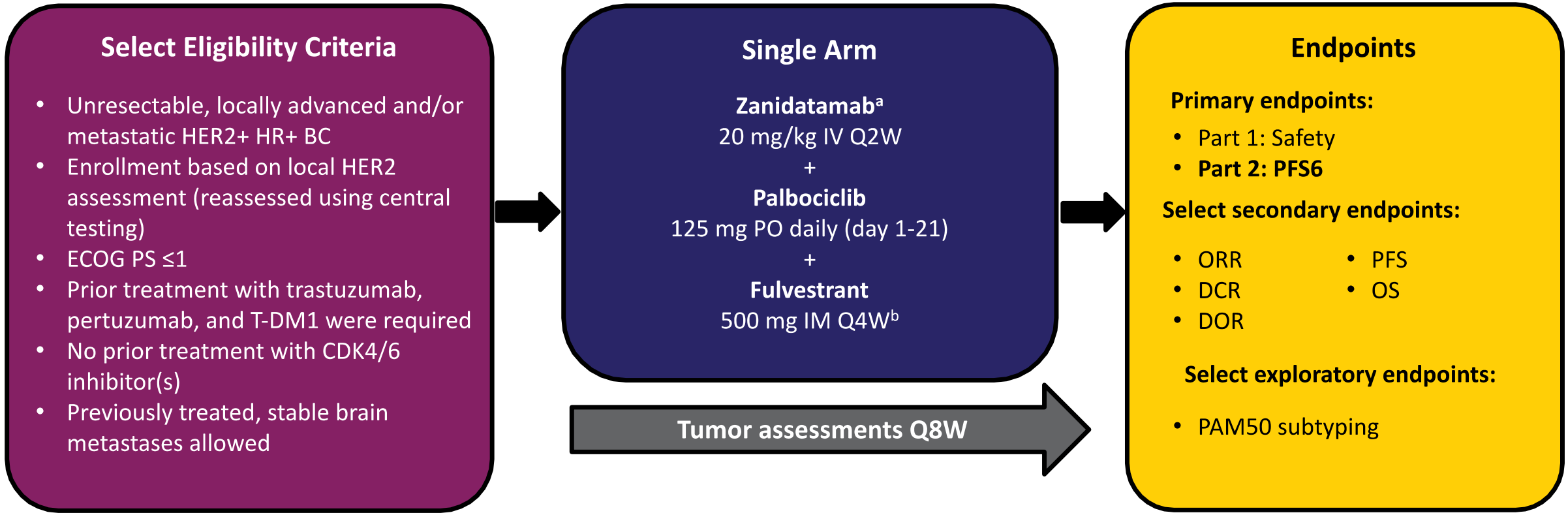
	Baseline (n=30)	Week 2 (n=25)	Surgery (n=22)
Geometric mean (SD)	31.9 (15.7)	4.3 (15.0)	12.1 (20.0)
Mean change 95% CI	–	–24.0 (–31.0; –7.1)	–10.9 (–19.3; –2.6)
Paired T-test P-value	–	–7.11 < 0.0001	–2.72 0.013





Gianni L, et al. Lancet Oncol 2018

Study Design: Phase 2a study (NCT04224272)



- Part 1 of the study evaluated safety and was previously reported (n=45); no zanidatamab-related DLTs occurred and the RDs for part 2 were identified[1,c]

[a]Mandatory infusion-related reaction prophylaxis (acetaminophen, diphenhydramine, and corticosteroids [hydrocortisone or dexamethasone]). [b]After loading doses of 500 mg IM on days 1, 15, 28. [c]One DLT of grade 4 neutropenia lasting >7 days occurred and was related to palbociclib.

1. Escrivá-de-Romani S, et al. Presented at San Antonio Breast Cancer Symposium 2022. Poster presentation [PD18-10].

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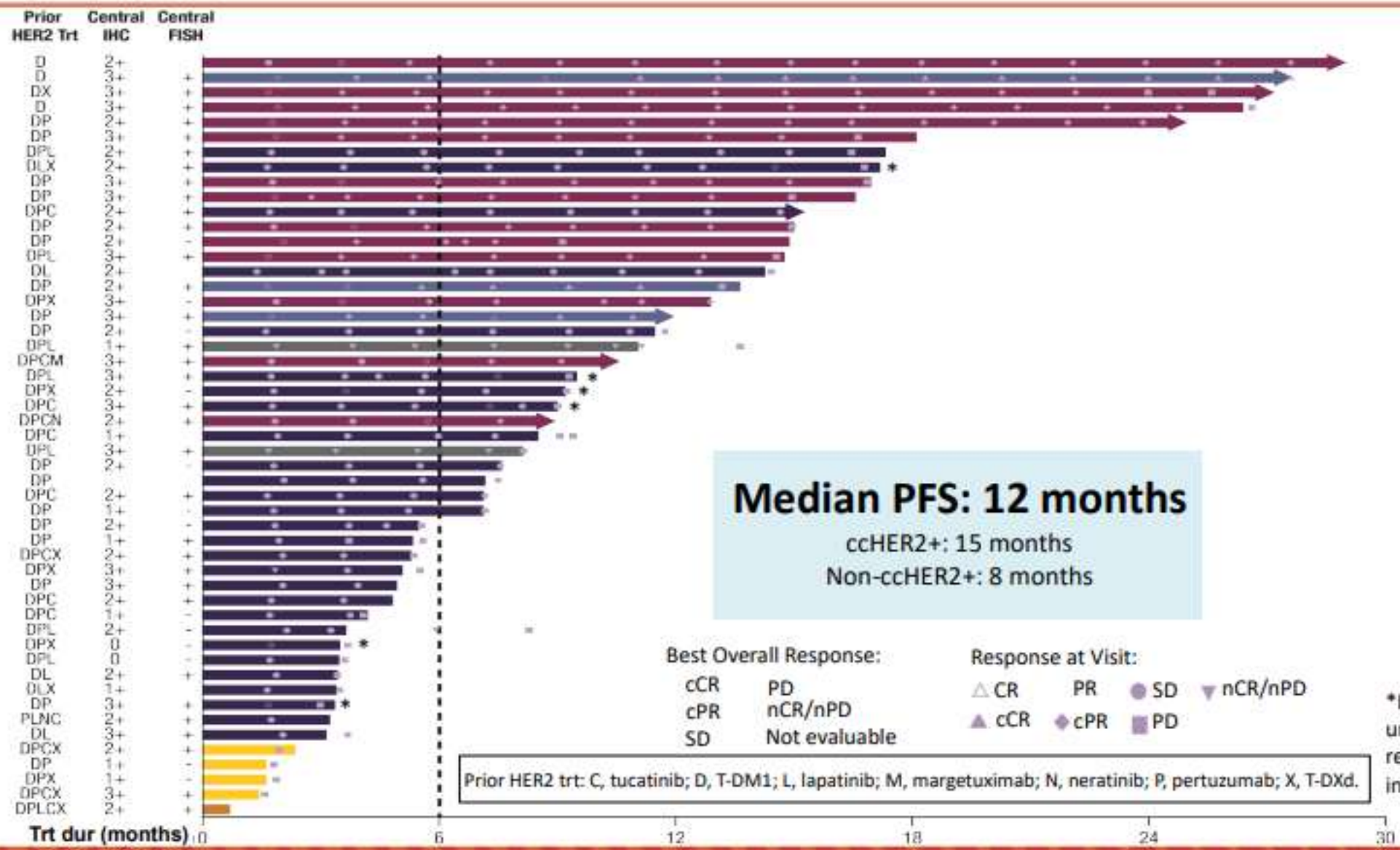
Treatment Duration and PFS



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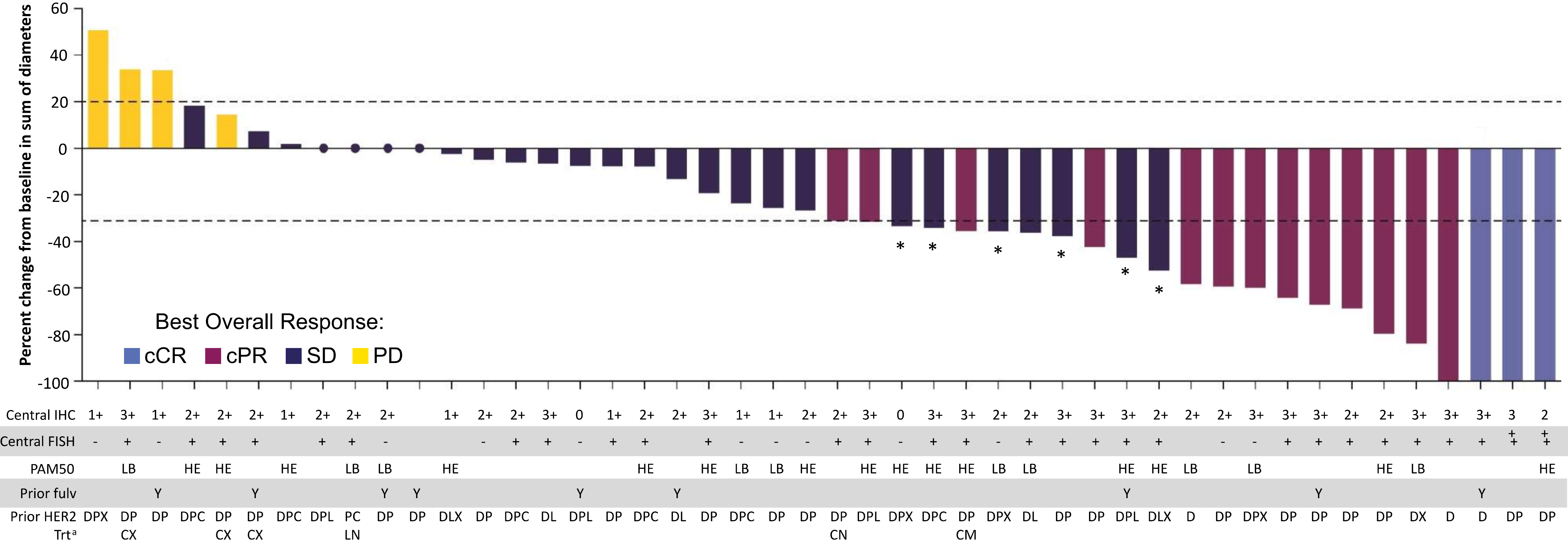
Efficacy of Treatment by Best Overall Response (All Patients With Measurable Disease)



Prior HER2 trt[a]: C, tucatinib; D, T-DM1; L, lapatinib; M, margetuximab; N, neratinib; P, pertuzumab; X, T-DXd.

PAM50 subtype: HE, HER2-enriched; LB, luminal B.

*Indicates patients with unconfirmed partial responses. Dotted lines indicate -30% and +20% change in tumor size.

[a]All patients received prior trastuzumab and taxane.

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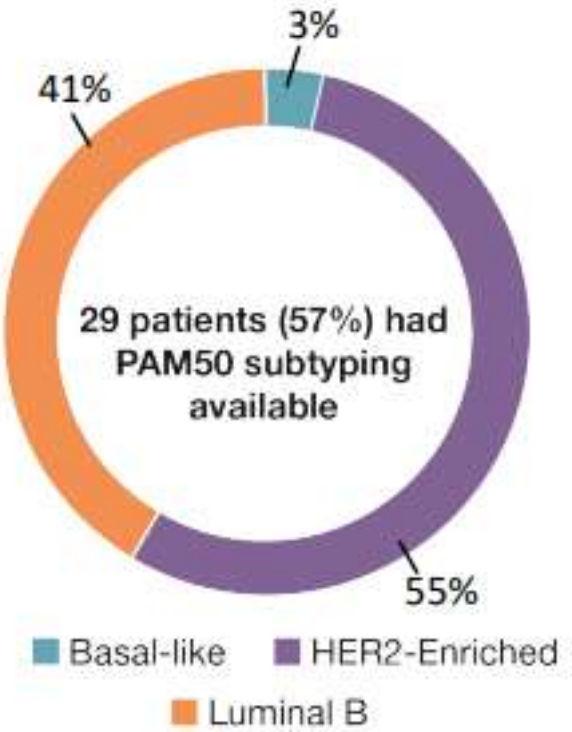
Efficacy of Treatment by PAM50 Subtype

	All Patients With PAM50 Subtyping (n=29)	Basal-Like (n=1)[a]	HER2-Enriched (n=16)	Luminal B (n=12)
PFS6, n (%) [95% CI]	19 (**66**) [46, 82]	1 (**100**) [2, 100]	10 (**62**) [35, 85]	8 (**67**) [35, 90]
Median PFS, months (95% CI)	9 (7, 14)	6 (NE, NE)	9 (4, 15)	12 (3, 24)
cORR, n (%)[b]	7 (28)	0	4 (27)	3 (30)
cBOR, n (%)[b]				
CR	1 (4)	0	1 (7)	0
PR	6 (24)	0	3 (20)	3 (30)
SD	16 (64)	0	10 (67)	6 (60)
PD	2 (8)	0	1 (7)	1 (10)
DCR, n (%) [95% CI][b]	23 (92) [74, 99]	0	14 (93) [68, 100]	9 (90) [56, 100]
Median DOR, months (95% CI)[c]	22 (12, NE)	0	13 (12, NE)	NE (22, NE)



- Compared with HER2-enriched, luminal B mBC was associated with numerically, but not statistically significant, longer median PFS (12 vs 9 months; *P*=0.74) and similar PFS6 (67% vs 62%)
- The cORRs for patients with HER2-enriched or luminal B mBC were numerically similar

[a]This patient did not have measurable disease. [b]Evaluated in patients with measurable disease (n=25 all patients with PAM50 subtyping; n=15 HER2-enriched; n=10 luminal B). [c]Evaluated in patients with CR or PR (n=7 all patients with PAM50 subtyping; n=4 HER2-enriched; n=3 luminal B).

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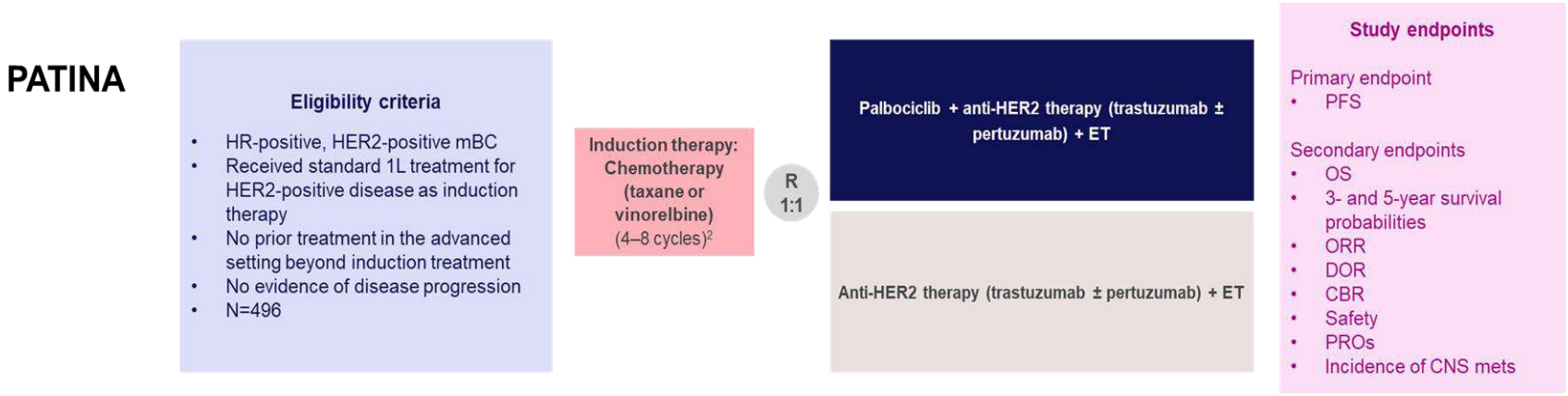
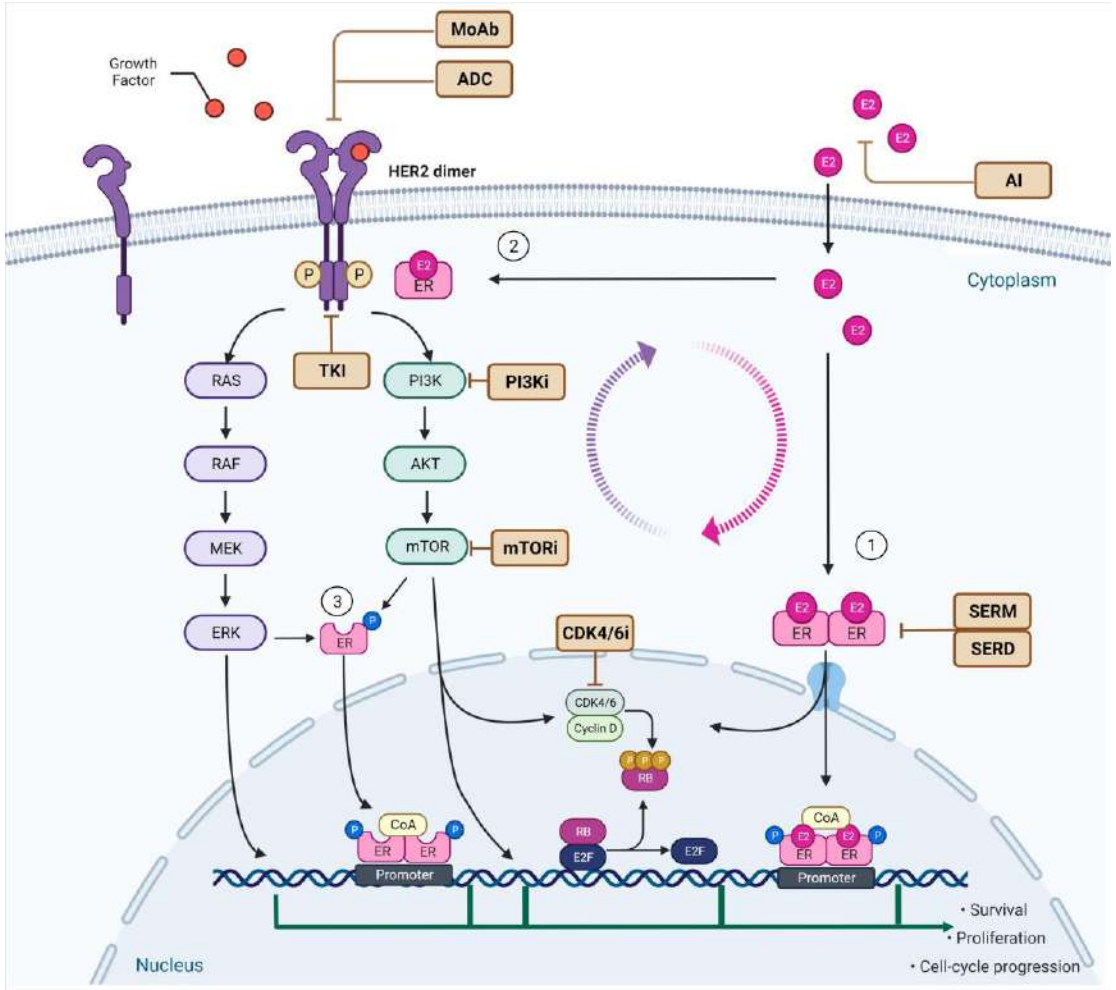
TARGETING CDK 4-6 PATHWAY



OUTLINE

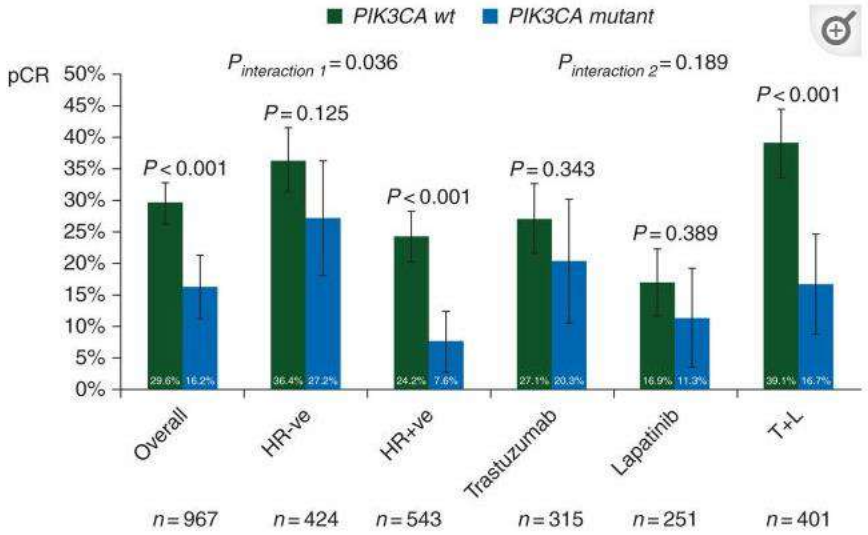
Targeting PD-L1
Targeting ER
Targeting mTOR
Targeting CDK 4-6
Targeting PIK3CA

TARGETING PIK3CA



TARGETING PIK3CA

Figure 1.



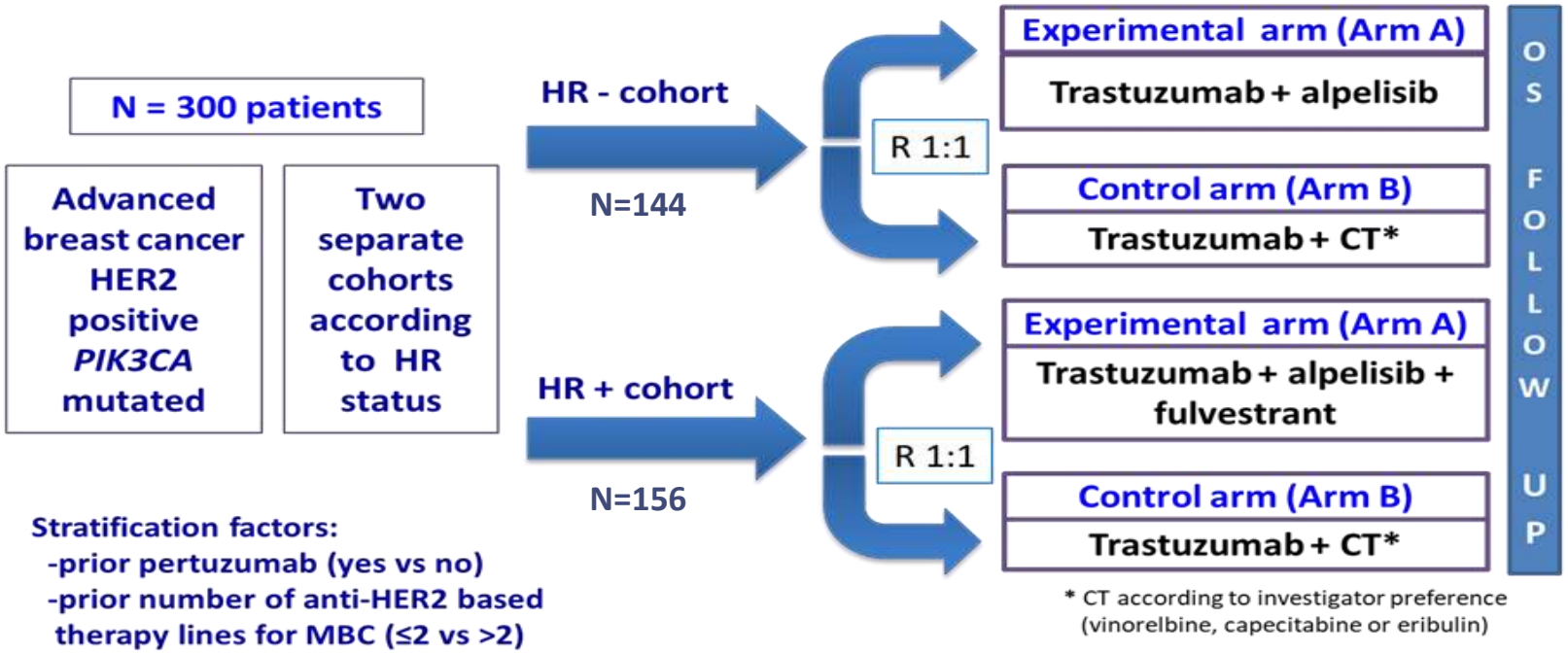
Pathological complete response rates according to *PIK3CA* mutation status overall, by HR status and anti-HER2 treatment.

Loibl et al , Ann Oncol. 2018 Apr 1;29(4):1075.

Alphabet

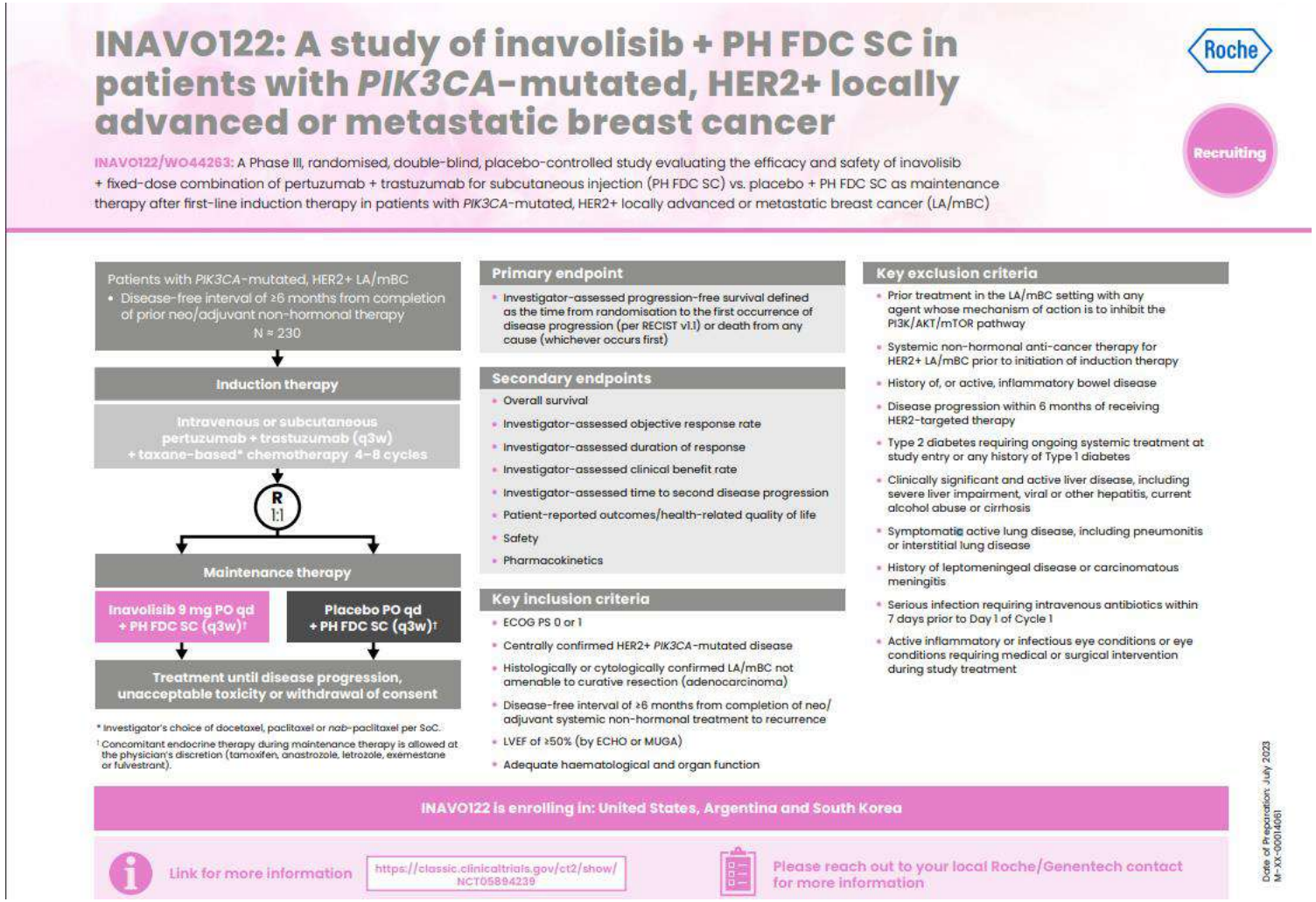
International, multicentre, open-label, phase III randomized trial

Central screening of *PIK3CA* mutations on the most recent available formalin-fixed paraffin-embedded (FFPE) tumor sample.



CT: chemotherapy, ctDNA: circulating tumor deoxyribonucleic acid, EOT: end of treatment, HER2: human epidermal growth factor receptor 2, HR: hormone receptor, MBC: metastatic breast cancer, OS: overall survival, PD: progressive disease, *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene, R: randomization.

TARGETING PIK3CA



CONCLUSIONS

- Enforcement of upfront and maintenance regimens with agents targeting signaling pathways involved in resistance to HER2-agents, ET, or both, may further improve clinical outcomes.
- Genomics and multi-omics tools may further dissect the biology of HER2-positive tumors to portend treatment personalization, involving the use of novel targeted agents, chemotherapy-free regimens, and possibly antibody-drug conjugates.
- Research is needed to further establish biomarkers mirroring the underlying tumor biology, to embrace treatment regimens in a biomarker-driven fashion and to extend be-yond a one-size-fits-all approach to HER2-positive tumors

ESMO DEEP DIVE: BREAST CANCER

Thank you to my team!

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ESMO WEBINAR SERIES

ESMO DEEP DIVE:
BREAST CANCER

WHAT'S THE ROLE OF THE MOLECULAR TUMOR BOARD ? EMERGING CONCEPTS

Barbara Pistilli, MD

Breast Cancer Unit

Gustave Roussy

France

ESMO WEBINAR SERIES

ESMO

DECLARATION OF INTERESTS

- **Barbara Pistilli, MD**

- **Consulting fees:** Astra Zeneca (institutional), Seagen (institutional), Gilead (institutional), Novartis (institutional), Lilly (institutional), MSD (institutional), Pierre Fabre (personal), Daiichi Sankyo (institutional/personal)
- **Research funding (to my institution):** Astra Zeneca, Daiichi Sankyo, Gilead, Seagen, MSD
- **Travel support:** Astra Zeneca; Pierre Fabre; MSD; Daiichi Sankyo, Pfizer

PLAN

Is there a role for the molecular tumor board in HER2-positive ABC ?

1. **Genomic profiling of HER2-positive ABC: why, who ?**
    1. Large molecular screening programs in breast cancer
    2. Genomic heterogeneity of HER2+ breast cancer
    3. Key genomic targetable alterations: PIK3CAmut, ERBB2mut
    4. Current ESMO recommendations

2. **New assessments of HER2 expression to predict response to trastuzumab deruxtecan**

3. **Mechanisms of resistance to HER2-directed therapies to guide further treatment choice**

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HER2-POS ABC ACROSS MOLECULAR SCREENING PROGRAMS

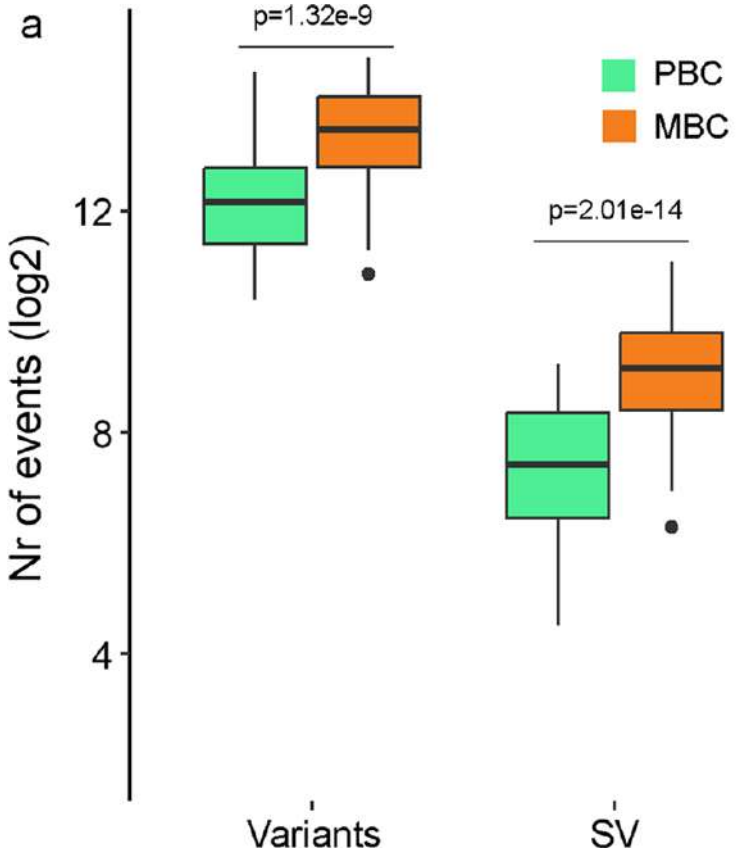
Study	Ref	Sample/assay	N	n, (%) HER2-positive	Molecular alterations
Plasma MATCH	Turner et al, Lancet Oncol 2020	ctDNA/ddPCR, Guardant360	1051	HR+: 65 (6.2) HR-: 36 (3.4)	ESR1: 3, ERBB2:2, AKT1:1 HER2:4
CATCH	Hlvenjak et al, JCO PO 2021	Tumor/WGS and transcriptome sequencing	127	HR+: 6 (5.55) HR-: 6 (5.55)	NA
SOLTI-1301 AGATA	Pernas et al, Front Oncol 2021	Tumor/TGS	305	HR+:22 (8.5) HR-: 8 (3.1)	ERBB2, ESR1, PIK3CA, TP53, AKT1
AURORA	Aftimos et al, Cancer Discovery 2021	Tumor, ctDNA/TGS, RNA-seq	381	HR+/HR-: 60 (16)	RB1, PIK3CA, TP53, ERBB2, NTRK1
SAFIR01	André et al, Lancet Oncol 2014	Tumor/CGH	423	HR+/HR-: 69 (16)	NA

HER2+ ABC has been included in most of the large molecular screening programs, however it accounts for about 10% of sequenced samples; described genomic alterations are consistent across the different programs

TGS: targeted gene-sequencing; NA: not available for the specific HER2-positive group

GENOMIC PROFILING OF HER2+ ABC

Comparison of metastatic with primary breast cancer



Verschoor et al, Breast Cancer Res 2023

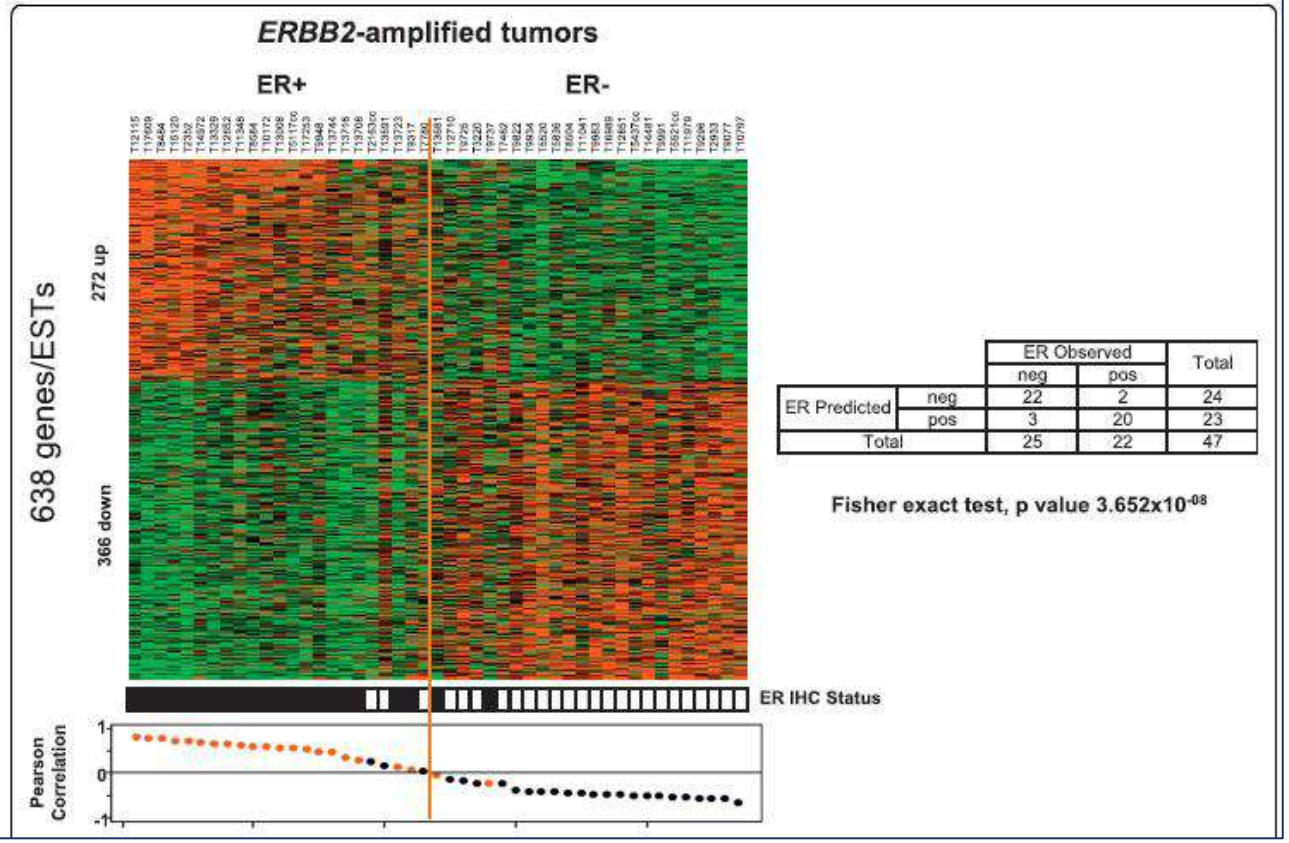
- WGS and RNA-seq n= 700 ABC, 68 HER2+
- **Higher number somatic nucleotide variants and a higher number of SVs in MBC as compared to PBC**
- **Higher TMB (p-value:0.003)**
- Higher frequency TP53mut (p-value: 0.028) regardless of ER status, but enrichment in p53mut was observed across all breast cancer subtypes
- Higher frequency ERRB2mut, no statistically significant (adj p-value: 0.35)

No specific genomic differences between primary and metastatic HER2+ breast cancer

SV: structural variants

GENOMIC PROFILING OF HER2+ ABC

Comparison of ER+ and ER- breast cancer



		ER Observed		Total
		neg	pos	
ER Predicted	neg	22	2	24
	pos	3	20	23
Total		25	22	47

Fisher exact test, p value 3.652×10^{-08}

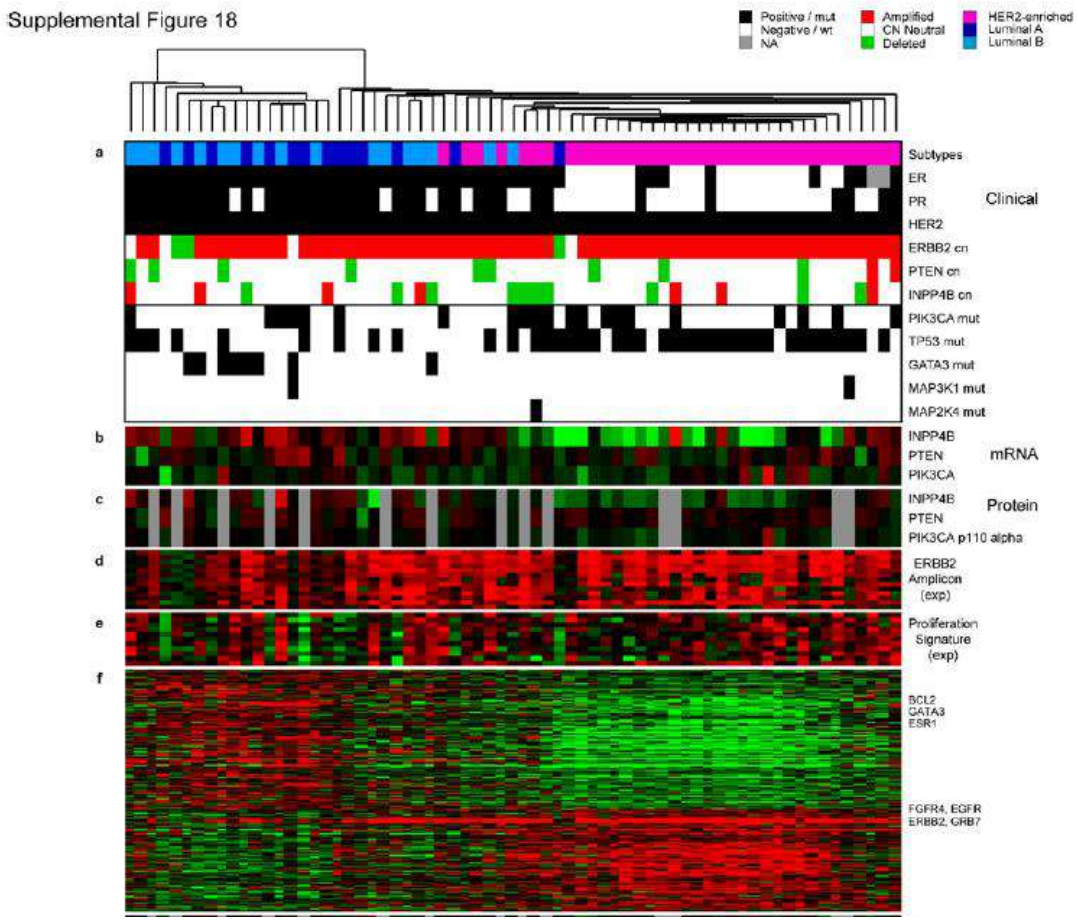
- N=54, aCGH + gene expression analysis
- 402 genes were differently expressed in ER+ vs ER- BC: GATA3, ESR1, TFF1, TFF3 and ERBB4 were upregulated; IGF2R, GATA6, EGFR and TGFA were downregulated in ER+ ERBB2-amplified tumors.

Some differences in the gene expression profile of ER+ and ER- HER2-amplified breast cancer

Sircoulomb et al, BMC Cancer 2010

GENOMIC PROFILING OF HER2+ ABC

Comparison of HER2E-mRNA/HER2+ and luminal-mRNA/HER2+

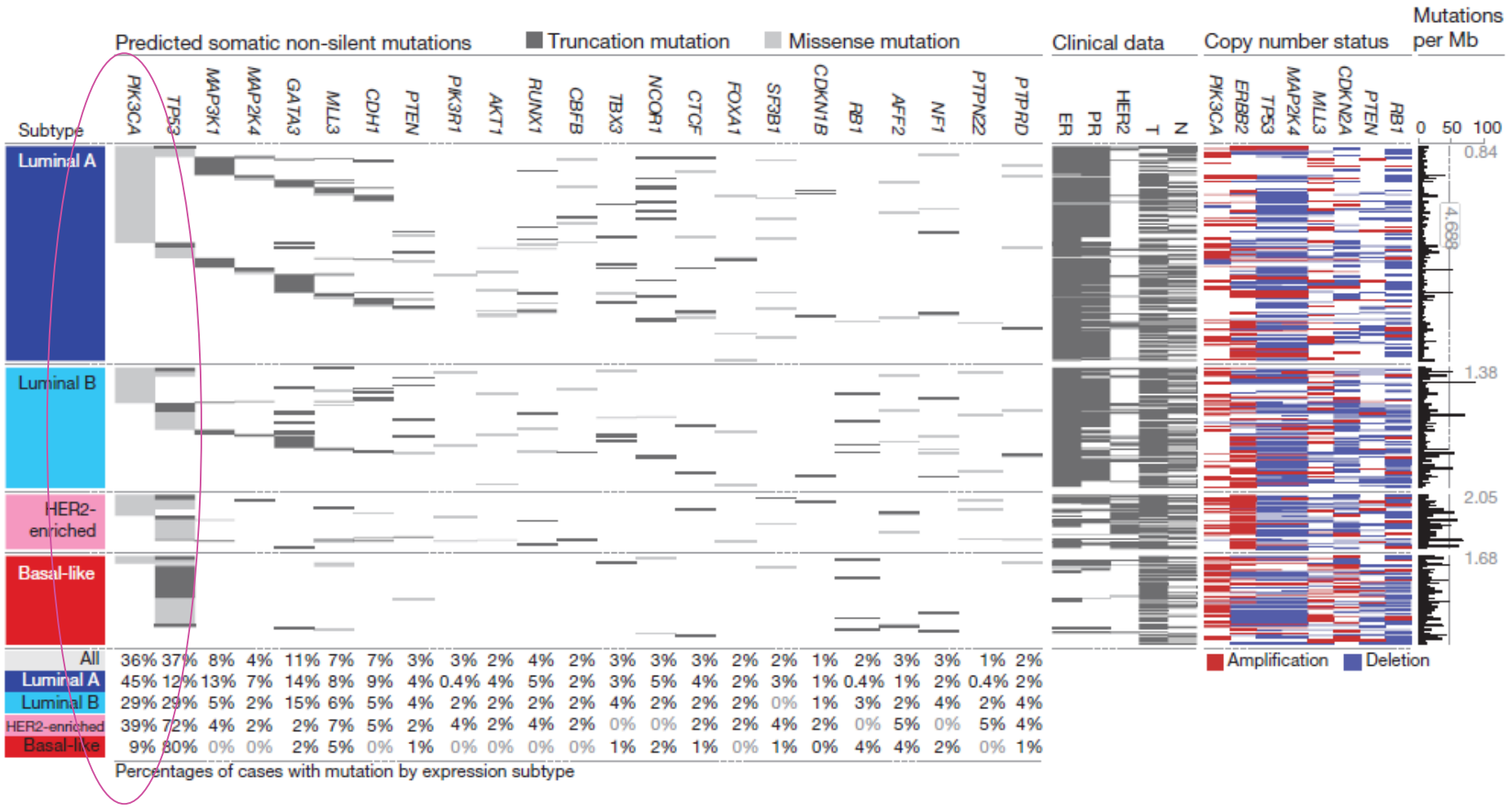


The Cancer Genome Atlas Network, Nature 2012

- not all clinically HER2+ tumors are HER2E mRNA subtype, and not all HER2E mRNA tumors are clinically HER2+: 50% of clinically HER2+ tumors are HER2E-mRNA-subtype
- **HER2E-mRNA-subtype/HER2+ tumors:** significantly higher expression of RTKs such as FGFR4, EGFR, ERBB2;
- **Luminal-mRNA/HER2+:** higher expression of GATA3, BCL2 and ESR1

Differences in the gene expression profile of HER2E-mRNA and luminal-mRNA HER2+ breast cancers

KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC



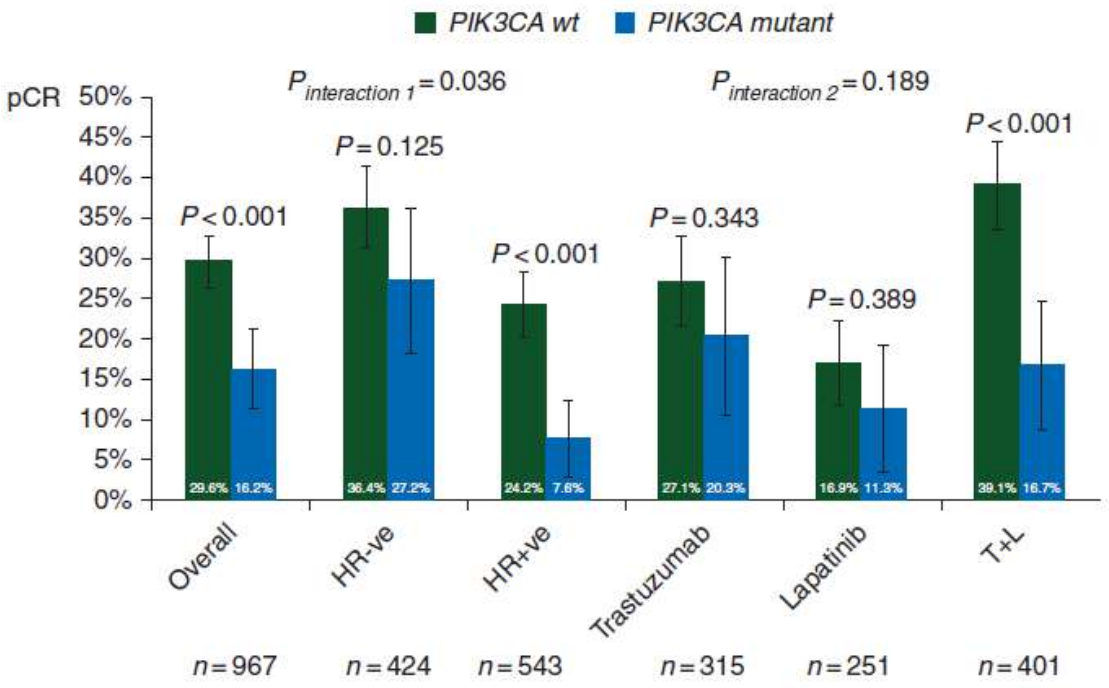
- N= 510 tumor samples, n= 72 HER2+
- Targetable somatic mutations: **PIK3CA (39%),** HER2mut (2.8%)

The Cancer Genome Atlas Network, Nature 2012

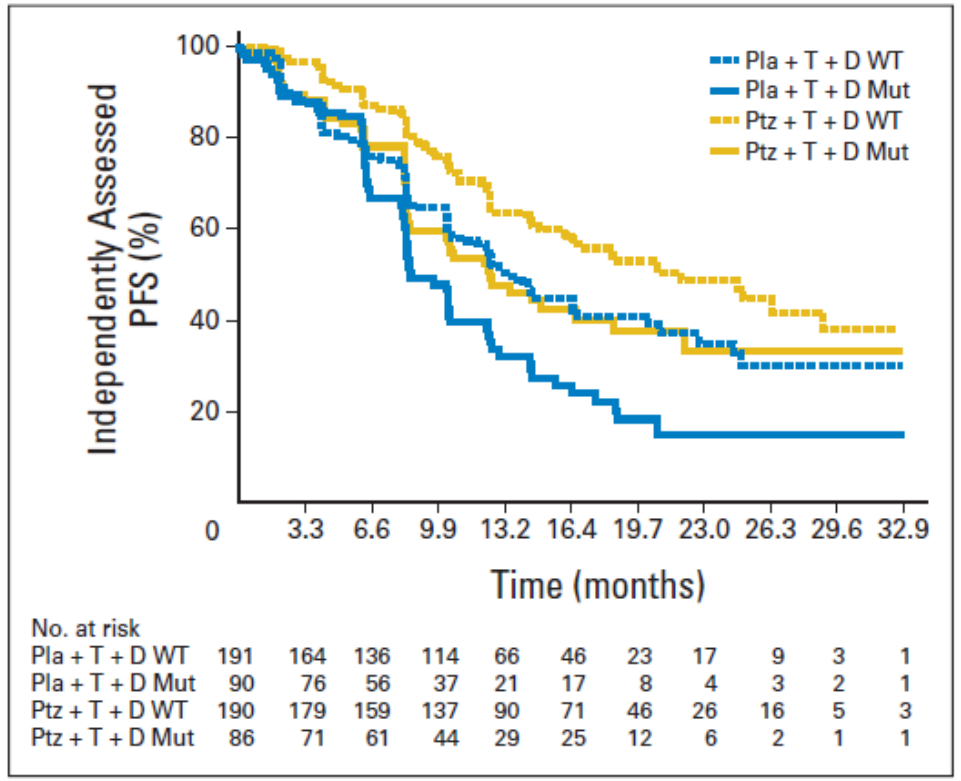
KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC

PIK3CA mutations are associated with worse survival outcomes and resistance to HER2-directed therapies

Lower rate of pCR in HER2+ EBC



Shorter PFS regardless of HER2-targeted therapy



Verschoor et al, Breast Cancer Res 2023; Loibl et al, Ann Oncol 2016; Baselga et al, JCO 2014

KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC

PI3Kinh in patients with HER2-positive ABC

Trial	Treatment	N	Results
NCT02038010 Phase I	Alpelisib + T-DM1	17	ORR =43% CBR = 71%
NCT01132664 Phase Ib/II	Buparlisib + trastuzumab	50	ORR = 10%
NCT03767335 Phase Ib	MEN1611+ trastuzumab+fulvestrant	42	ORR = 9/29

They did not select patients with PIK3CA-mutated tumors

Jain et al, ASCO 2017; Pistilli et al, BCRT 2018; Piccart et al, ESMO 2021

KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC

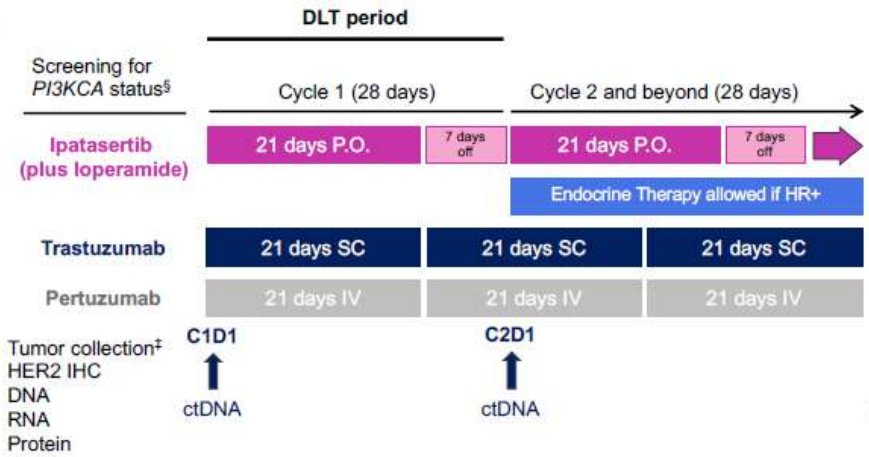
Promising activity of AKTinh in HER2-positive ABC ?

SOLTI-1507 IPATHER: STUDY DESIGN

Open-label, single-arm, phase Ib trial (NCT04253561)

Key eligibility criteria

- Pre/post menopausal women or male
- HER2-positive† ABC
- *PI3KCA*mut in tissue or plasma†
- Prior treatment with CT* + HP for ABC in the first line setting
- No evidence of PD



SOLTI

Primary Endpoints:
- MTD and RP2D

Secondary Endpoints:
- Safety and tolerability
- ORR and CBR
- PFS

RESULTS

Efficacy (N=16)

Efficacy	N = 16
Follow-up: median (95% CI), months	19.9m (9.3 - NR)
Confirmed ORR	31.3% (12.1 - 58.5)[a]
Best overall response	
CR	2 (12.5%)
PR	3 (18.7%)
SD ≥ 24 weeks / < 24 weeks	6 (37.5%) / 5 (31.3%)
PD	-
CBR (CR+PR+SD≥ 24 weeks*)	84.6% (53.7 - 97.3)[a]
DoR: median (95% CI), months	NR (12.1 - NR)
PFS (from enrolment), months	
Median (95%CI)	15.4 (9.4 - NR)
12-mo PFS (95%CI)	67.3% (45.3 - 100)
18-mo PFS (95%CI)	48.1% (26.0 - 88.8)

[a] 95% exact binomial confidence interval (by Clopper-Pearson method).

Oliveira et al, ESMO BREAST 2024

KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC

HER2-mutations vs HER2-amplification

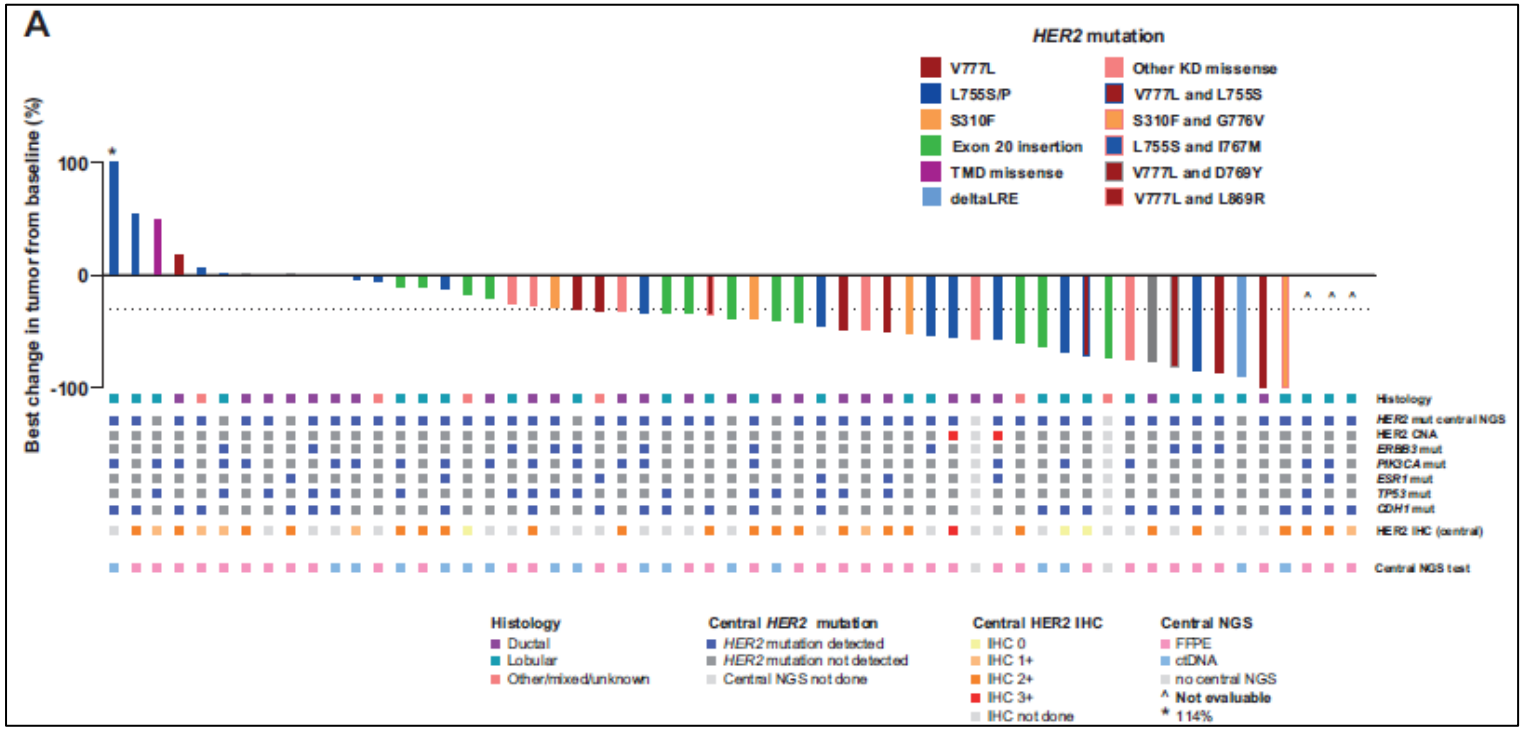
- 2-4% of all BC: HER2-neg/low BC > HER2-positive
- 8% in ER+ ABC
- 15% in metastatic ILC
- Most common ERBB2 hotspot mutations can activate the HER2 signaling pathway and have been associated with worse outcomes
- ERBB2 mutations have been identified also as a mechanism of acquired resistance to ER-directed therapies

Grinda et al, ESMO Open 2023; Jhaveri et al, Ann Oncol 2023; Wang et al, Cancer Science 2017

KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC

HER2-mutations vs HER2-amplification

SUMMIT TRIAL: cohort neratinib + fulvestrant + trastuzumab



- N=57 patients with ER+/HER2-/low MBC, previously treated with CDK4/6inh
- ORR: 39% [95% CI 26% ;52%]
- median PFS was 8.3 months [95% CI 6.0-15.1 months]

Jhaveri et al, Ann Oncol 2023;

KEY GENOMIC TARGETABLE ALTERATIONS IN HER2+ BC

list of genomic alterations level I/II according to ESCAT in ABC

Table 3. List of genomic alterations level I/II according to ESCAT in advanced breast cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
ERBB2	Amplifications	15%-20%	IA	Anti-HER2 monoclonal antibodies HER2 TKIs Anti-HER2 ADCs	Baselga et al., *N Engl J Med* 2012[55] Krop et al., *Lancet Oncol* 2014[56] Lin et al., *J Clin Oncol* 2020[57] Saura et al., *J Clin Oncol* 2020[58] Rugo et al., *JAMA Oncol* 2021[59]
	Hotspot mutations	4%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., *Nature* 2018[51] Smyth et al., *Cancer Discov* 2020[60] Li et al., *Ann Oncol* 2023[61]
PIK3CA	Hotspot mutations	30%-40%	IA (ER-positive HER2-negative ABC)	α-specific PI3K inhibitors*	André et al., *N Engl J Med* 2019[62] Rugo et al., *Lancet Oncol* 2021[63] Turner et al, *N Engl J Med* 2023[70]
ESR1	Mutations	30%-40%	IA (ER-positive HER2-negative ABC resistant to AI)	SERDs	Bidard et al., *J Clin Oncol* 2022[64] Bardia et al., *Cancer Res* 2023[65]
BRCA1/2	Germline pathogenic/likely pathogenic variants	4%	IA	PARP inhibitors	Litton et al., *N Engl J Med* 2018[66] Robson et al., *Eur J Cancer* 2023[67]
	Somatic mutations	3%	IIB	PARP inhibitors	Tung et al., *J Clin Oncol* 2020[68]
PTEN	Mutations/deletions	7%	I/II	AKT inhibitors	Schmid et al., *J Clin Oncol* 2020[69] Turner et al., *N Engl J Med* 2023[70]
AKT1	Mutations (p. E17K)	5%	I/II	AKT inhibitors	Kalinsky et al., *JAMA Oncol* 2021[71] Turner et al., *N Engl J Med* 2023[70]
PALB2	Germline pathogenic/likely pathogenic variants	1%	IIB	PARP inhibitors	Tung et al., *J Clin Oncol* 2020[68] Gruber et al., *Nat Cancer* 2022[72]

it is recommended NGS of a tumor (or plasma) sample in patients with **HR+/HER2-ABC** as standard of care, to be done after resistance to ET to optimize the likelihood of detecting ESR1 mutations.

Mosele et al, Ann Oncol 2024

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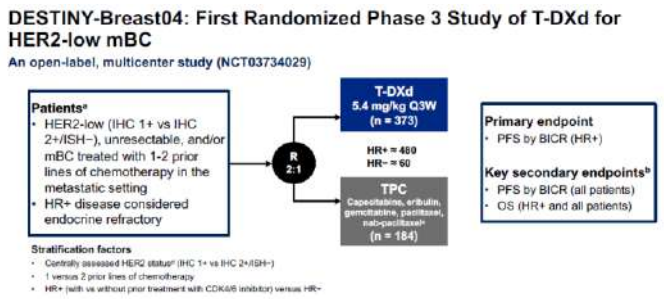
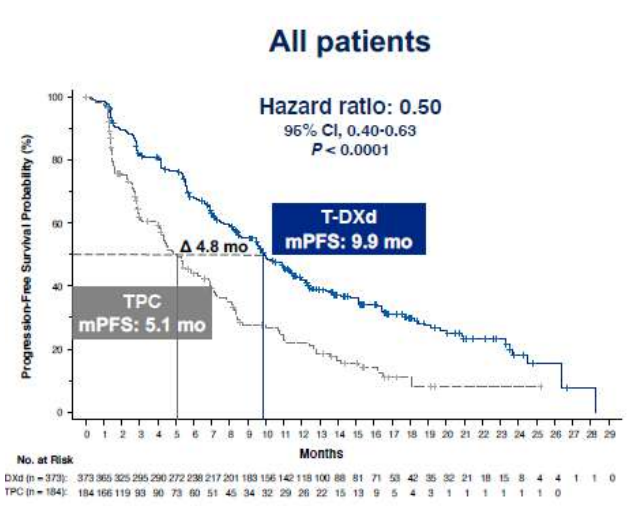
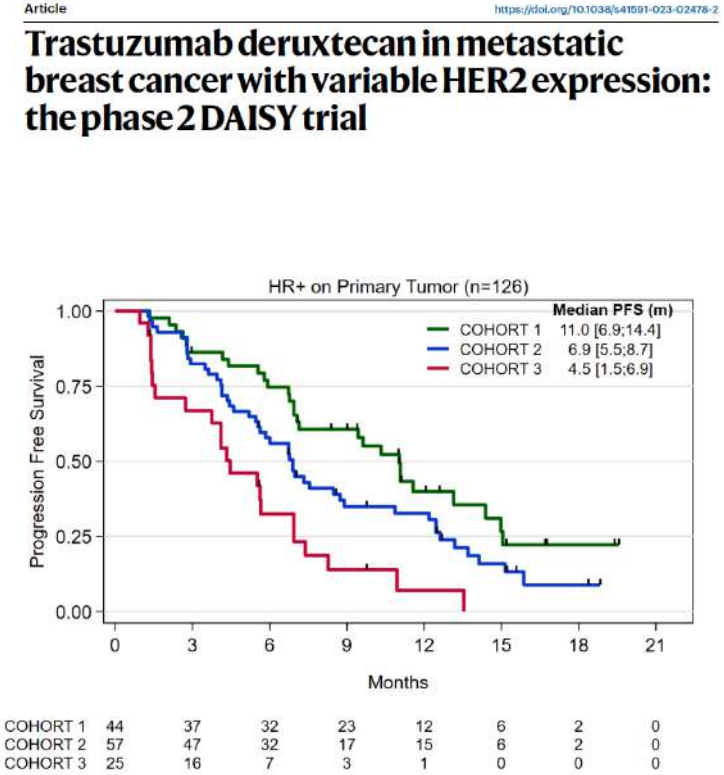
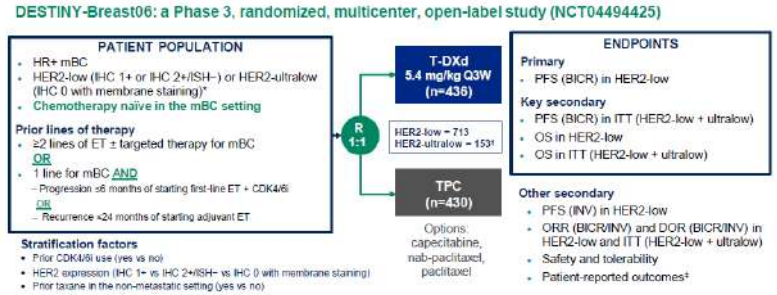
NEW ASSESSMENTS OF HER2 EXPRESSION

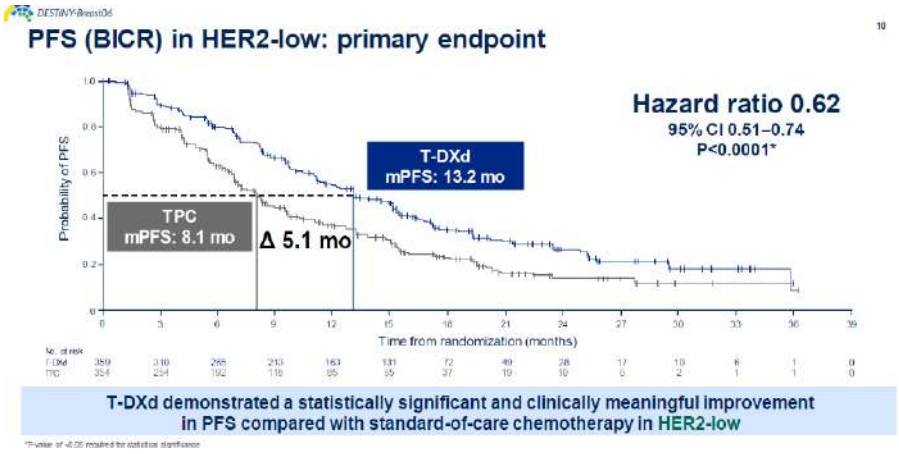
Trastuzumab deruxtecan showed activity across a wide range of HER2 expression levels







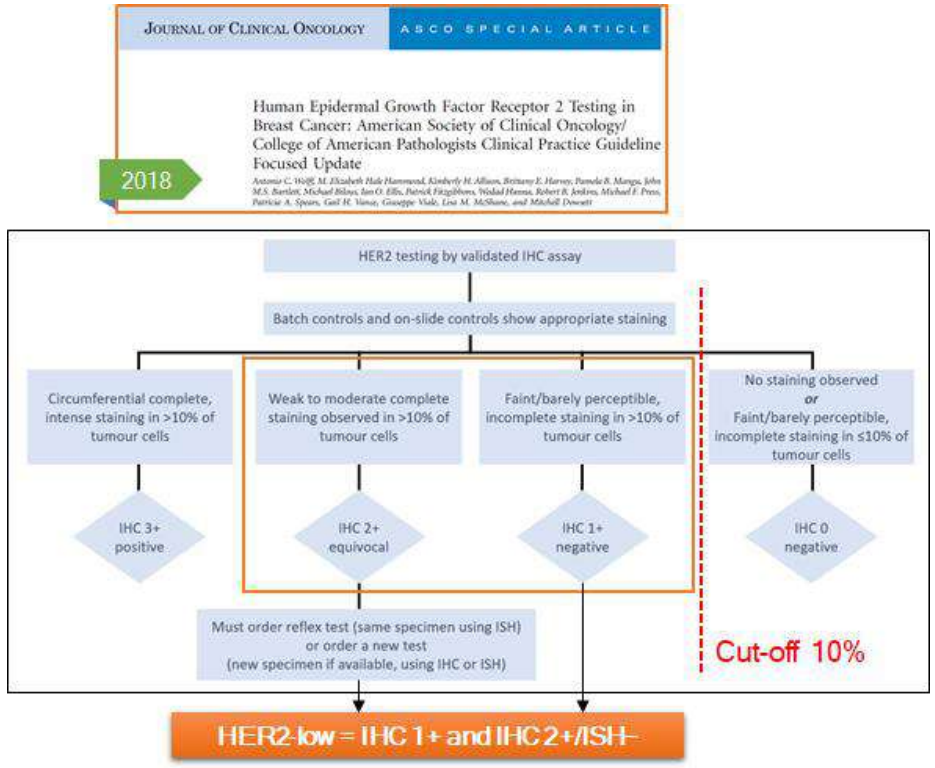




Modi et al, NEJM 2023; Mosele et al, Nature Medicine 2023; Curigliano et al, ASCO 2024

NEW ASSESSMENTS OF HER2 EXPRESSION

Raising the question whether standard IHC and current scoring is the optimal way to predict sensitivity to trastuzumab deruxtecan



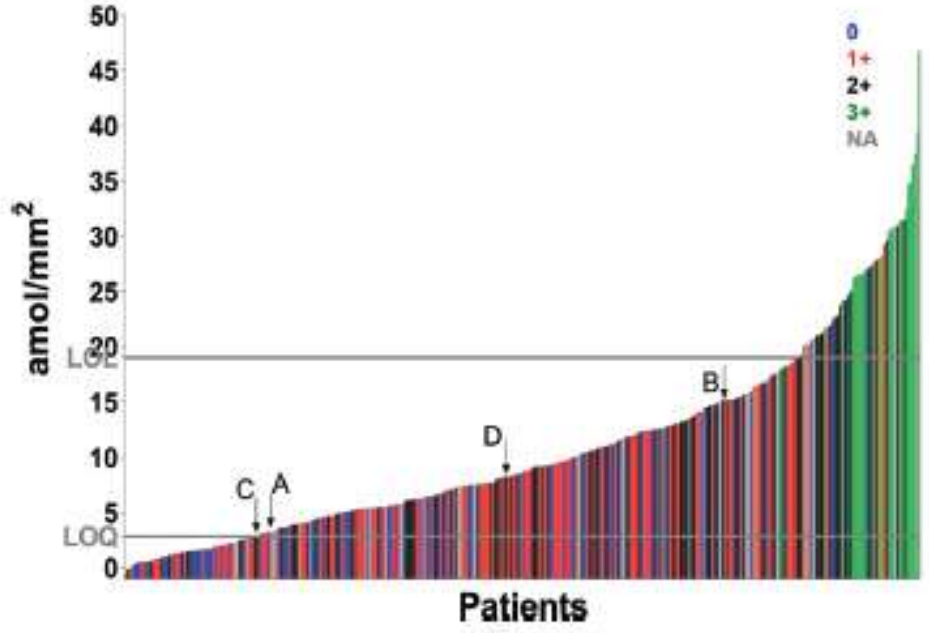
The available HER2 IHC assays are designed to differentiate between HER2-overexpressing BCs that can benefit of trastuzumab and those that are not HER2-overexpressing

Wolff et al, JCO 2018; Wolff et al, JCO 2023

NEW ASSESSMENTS OF HER2 EXPRESSION

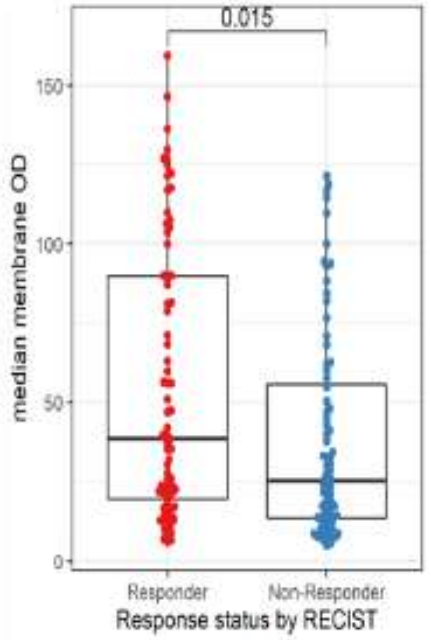
Do we need new “more quantitative” methods to assess HER2 expression ?

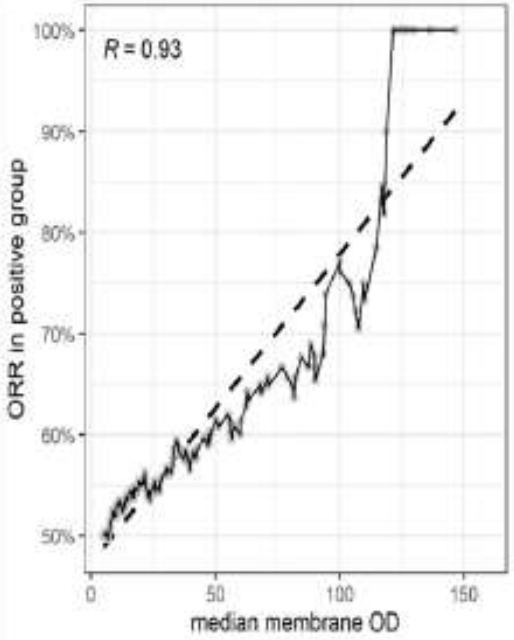
quantitative immunofluorescence coupled with mass spectrometry **<u>to measure absolute amounts of HER2 protein</u>**: 67% of patients had HER2 expression, but would have been considered negative by standard IHC



Moutafi et al, Laboratory Investigations 2022; Kapil et al, Scientific Reports 2024

<u>Quantification of HER2 protein expression</u> as measured by optical density (OD) in the membrane and the cytoplasm of each tumor cell by using deep-learning–based image analysis (IA) of digitized tissue sections better predicted response to T-DXd as compared to manual IHC





NEW ASSESSMENTS OF HER2 EXPRESSION

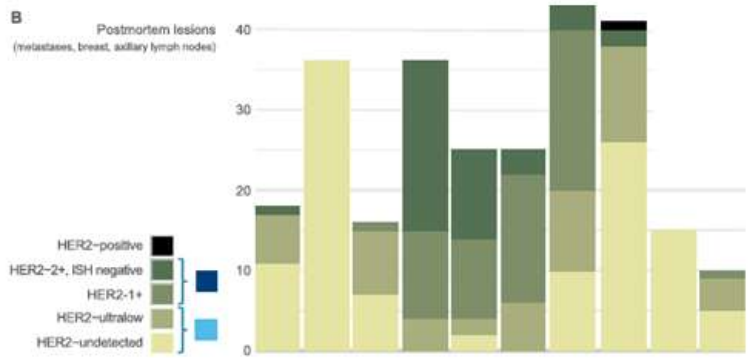
Heterogeneity of HER2 expression can also affect treatment response

INTRA-TUMOR AND INTER-METASTASES HER2 HETEROGENEITY

Cluster with prevalence of HER2-neg areas -> no response to T-DXd

INTRATUMOR TARGET SPATIAL DISTRIBUTION AFFECT RESPONSE TO T-DXd !

8/10 patients: inter-metastasis heterogeneity of HER2 status



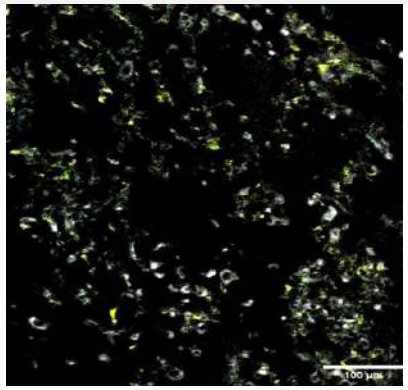
DOES IT AFFECT RESPONSE TO T-DXd ?

Modified from Pistilli, ASCO 2023; Mosele et al, Nature Medicine 2023; Geukens et al, EJC 2023

NEW ASSESSMENTS OF HER2 EXPRESSION

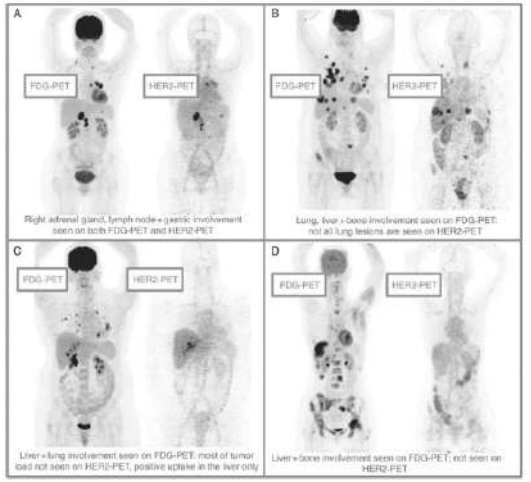
New technologies for capturing intratumor and inter-metastases HER2 heterogeneity

**Spatial technologies for multiple protein analysis-
AI digital pathology**



Better quantification of HER2 expression and characterization of HER2 spatial distribution

Ab-radiolabeled PET scan



Inter-metastases heterogeneity of HER2 expression

Modified from Pistilli, ASCO 2023. Imaging mass cytometry (Hyperion) on BC metastases (personal data); Gebhart et al, Ann Oncol 2016

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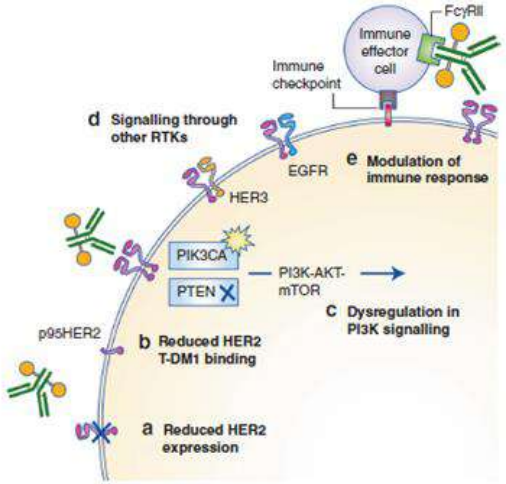
MECHANISMS OF RESISTANCE TO HER2-DIRECTED THERAPIES TO GUIDE FURTHER TREATMENT CHOICE

Potential mechanisms of resistance to T-DM1

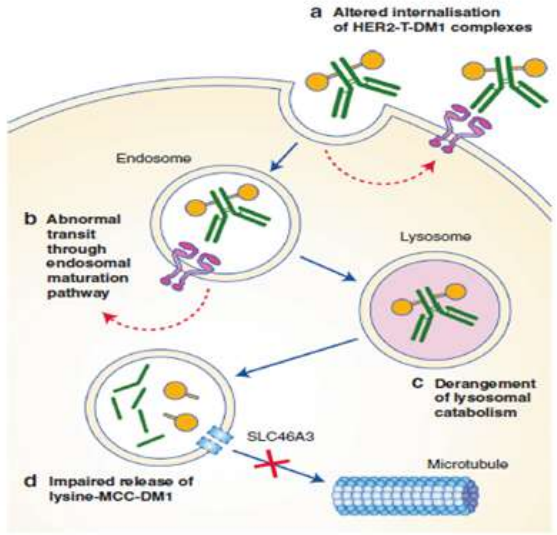
Decreased HER2 expression ->T-DM1-resistant JIMT-1, HCC1954-TM, BT-474-TM lines

Reduced T-DM1 binding -> T-DM1 resistant NCI-N87 human GC line



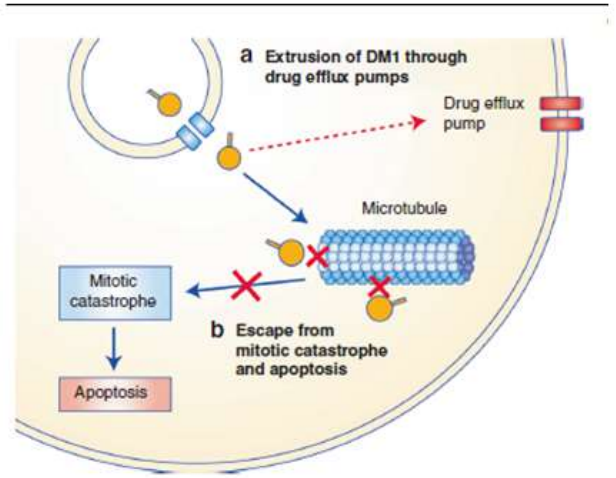
Altered T-DM1 internalization and intracellular trafficking:

- enhanced endosomal recycling of HER2-T-DM1 complex-> T-DM1-resistant JIMT-1 BC cell lines
- higher expression of caveolin-1 and protein involved in vesicle transport-> T-DM1-resistant NCI-N87 GC cells (conflicting results)
- impaired lysosomal functions-> T-DM1-resistant NCI-N87 GC cells, T-DM1-resistant BT-474



Reduced payload activity:

- upregulation of MRP1-efflux transporters > T-DM1-resistant NCI-N87 GC, BT-474, KPL-4, SKBR3 cell lines
- mitotic slippage -> T-DM1-resistant SK-BR-3 and BT-474 cells



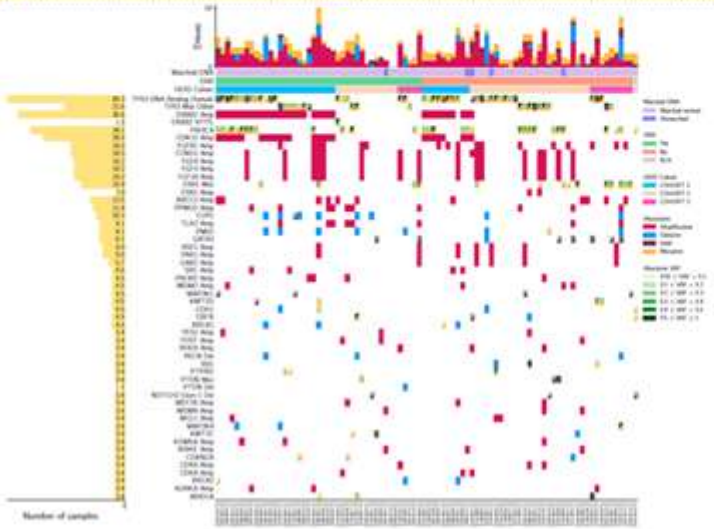
Hunter et al, 2020; Loganzo et al, 2015; Sabbaghi et al, 2017; Li et al, 2018; Wang et al, 2017; Rios-Luci et al, 2017; Kinner et al, 2018; Saatci et al, 2018

MECHANISMS OF RESISTANCE TO HER2-DIRECTED THERAPIES TO GUIDE FURTHER TREATMENT CHOICE

Potential mechanisms of resistance to T-DXd

WES at baseline (n=88) and at progression (n=20)
ERBB2 hemizygous deletion was detected in 5 out of 88 (6%) patients at baseline-> no response

- 88 frozen tumor biopsies at baseline analyzed by whole exome sequencing (WES)
- 83 matched blood samples at baseline assessed by WES

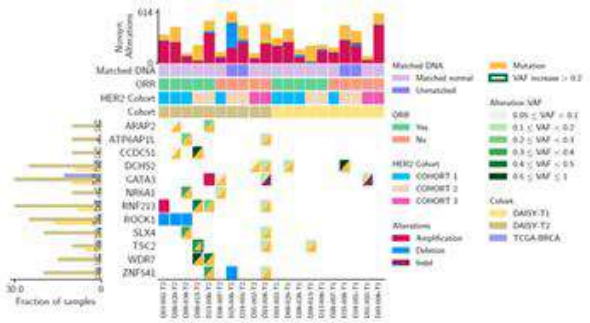


No recurrent driver alterations in baseline samples were associated with resistance

- **5/88 (6%) *ERBB2* hemizygous deletion**
- 4 of these patients did not response to T-DXd (2 with HER2-low and 2 with HER2-null mBC)

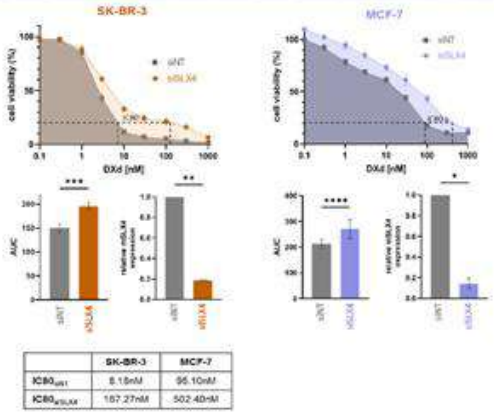
Mosele et al, Nature Medicine 2023

- 20 frozen tumor biopsies at progression analyzed by WES
- 10 samples with matched biopsy at baseline



- *SLX4* encodes a DNA repair protein that regulates endonucleases, whose role in camptothecin resistance remains unclear
- 4/20 (20%) *SLX4* mutation biopsies at progression
- 2 *SLX4* mutations were not detectable in baseline samples
- 2 *SLX4* mutations there was no matched baseline sample

- SK-BR-3 and MCF-7 BC cell lines depleted for *SLX4* by siRNA were treated with DXd during 5 days



	SK-BR-3	MCF-7
$IC80_{siNT}$	8.18nM	95.10nM
$IC80_{siSLX4}$	167.27nM	502.40nM

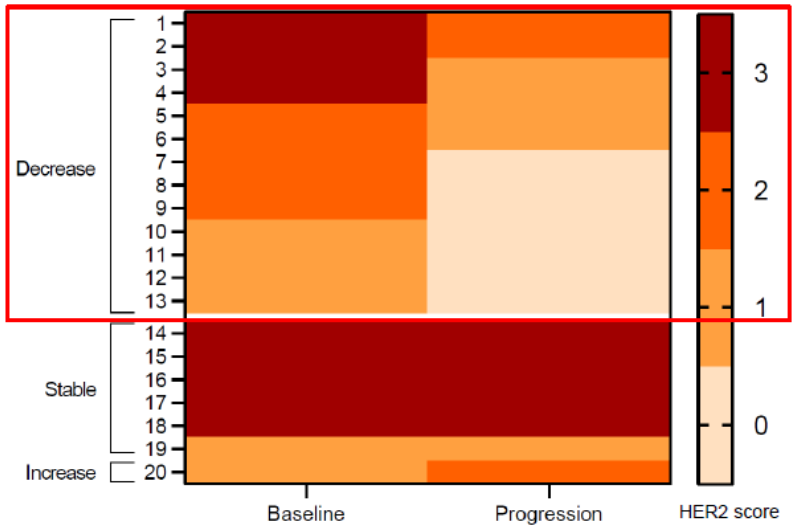
***SLX4* loss of function mutations could mediate resistance to DXd**

MECHANISMS OF RESISTANCE TO HER2-DIRECTED THERAPIES TO GUIDE FURTHER TREATMENT CHOICE

Potential mechanisms of resistance to T-DXd

Unsupervised ML-digital pathology: cluster with prevalence of HER2-neg areas (fibroblasts, immune cells, collagen fibers)-> no response

- 25 FFPE samples at baseline and progression: **9** HER2 IHC 3+ or IHC 2+/ISH+; **11** HER2 IHC 2+/ISH- or IHC 1+; **5** IHC 0
- HER2 status by standard IHC



13/20 (65%)
95% CI [40.8-84.6]

13 out of 20 (65%) patients presented a decrease of HER2 expression at progression

5 patients HER2 IHC 0: 4 stable and 1 to IHC

Mosele et al, Nature Medicine 2023

IS THERE A ROLE FOR THE MOLECULAR TUMOR BOARD IN HER2-POSITIVE ABC ?

Yes, I would say rather for a **MULTIOMICS tumor board**

- **Genomic profiling of HER2-positive ABC** is currently not recommended by ESMO guidelines, however it remains an option for selecting patients eligible to novel targeted therapies in clinical trials after exposure to multiple lines of HER2-directed therapies

- **New technologies are being developed for the assessments of HER2 expression** to better predict response to trastuzumab deruxtecan: they will require trained and dedicated staff for the implementation and interpretation in standard practice

- **Mechanisms of resistance to HER2-directed therapies** are multiple, complex and require novel tools but also dedicated expertise for their use and interpretation in order to guide further treatment choice

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