Current and Evolving Approaches for HER2+ Breast Cancer Brain Metastases

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Disclosures

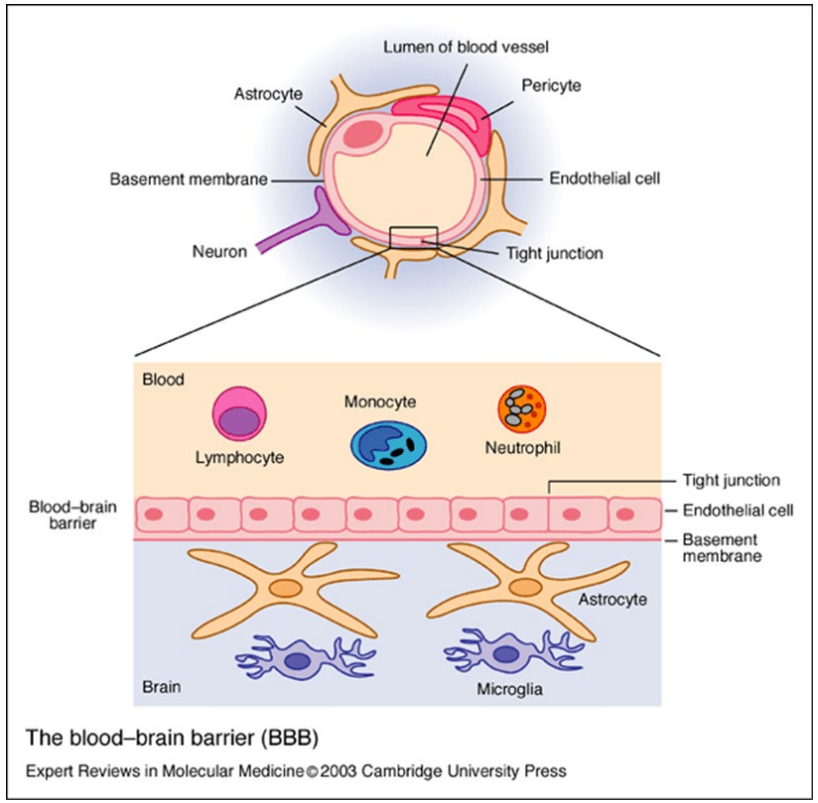
- Research funding PUMA, Lilly, Merck, Seattle Genetics, Nektar, Tesaro, G1-Therapeutics, ZION, Novartis, Pfizer, Astra Zeneca, Elucida, Caris, Incyclix, Beigene

- Honoraria: Genentech, Eisai, IPSEN, Seattle Genetics, Astra Zeneca, Novartis, Immunomedics, Elucida, Athenex, Roche

- Royalties: UpToDate, Jones and Bartlett

Breast Cancer Brain Metastases: Challenges Faced

- Devastating, feared and increasingly common consequence of breast cancer
  - Incidence 30% HER2+[1], 50% triple negative[2] advanced breast cancer
- Blood brain barrier, efflux pumps in brain endothelium limit exposure to cytotoxics
- Clinical trials frequently excluded patients with CNS disease
  - Few previous trials specifically targeting patients with brain metastases



The blood–brain barrier (BBB)

[1] *Bendell et al. Cancer 2003,* [2] *Lin et al. Cancer 2008*

NCCN: Systemic Therapy Options expanded in 2025 - 2026

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Brain Metastases

NCCN Guidelines Index
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Continued

Note: All recommendations are category 2A unless otherwise indicated.

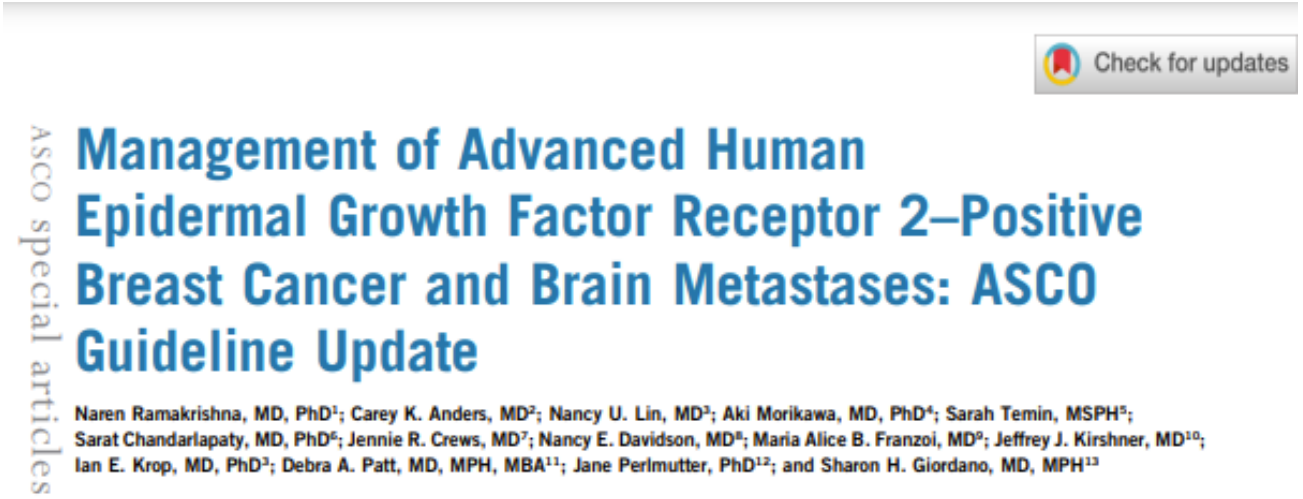
Strategies available:

HER2 TKIs:
Tucatinib
Neratinib
Pyrotinib (non-US)

Her2 targeting ADC's:
Trastuzumab Deruxtecan
TDM1

MoAb:
High-dose trastuzumab/ pertuzumab

Management of systemic therapy at first intracranial progression with stable extracranial disease



Check for updates

ASCO special articles

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

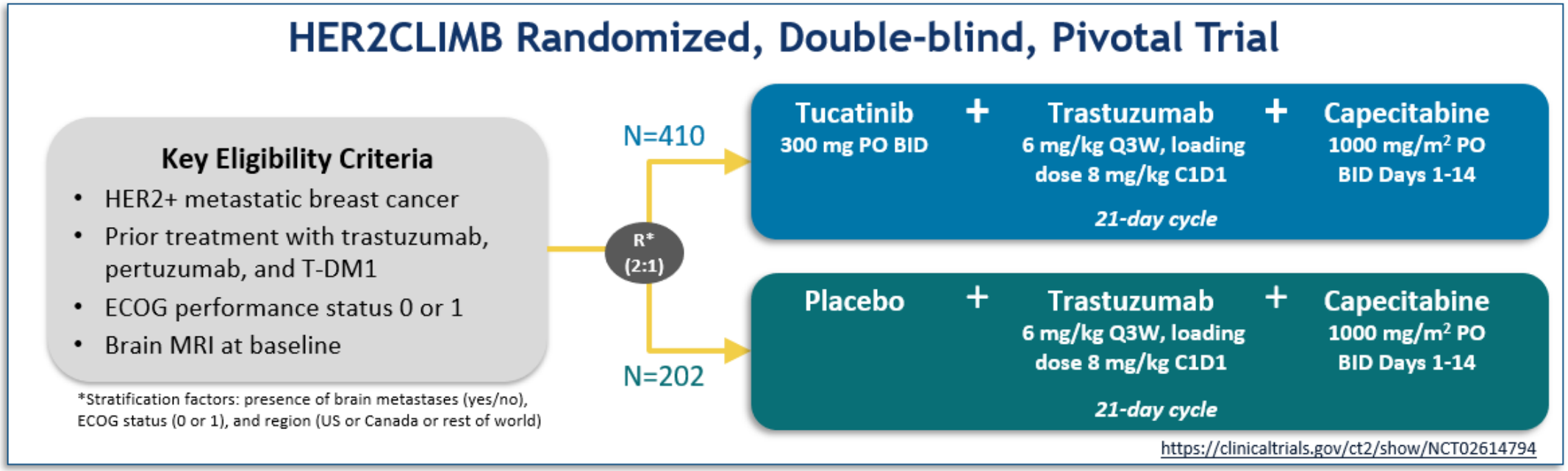
Naren Ramakrishna, MD, PhD[1]; Carey K. Anders, MD[2]; Nancy U. Lin, MD[3]; Aki Morikawa, MD, PhD[4]; Sarah Temin, MSPH[5]; Sarat Chandarlapaty, MD, PhD[6]; Jennie R. Crews, MD[7]; Nancy E. Davidson, MD[8]; Maria Alice B. Franzoi, MD[9]; Jeffrey J. Kirshner, MD[10]; Ian E. Krop, MD, PhD[3]; Debra A.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

- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched from their current HER2-targeted therapy regimen.
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.

HER2Climb Study Schema

Background

- Up to half of patients with HER2+ metastatic breast cancer may develop brain metastases and effective and tolerable treatment options are needed.[1-4]
- Tucatinib is an oral TKI, recently approved by the FDA, that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.[5-6]



1. Bendell JC, et al. Cancer 2003;97:2972-7.
2. Brufsky AM, et al. Clin Cancer Res 2011;17:4834-43.
3. Leyland-Jones B. J Clin Oncol 2009;27:5278-86.
4. Olson EM, et al. Breast 2013;22:525-31.
5. Moulder SL, et al. Clin Cancer Res 2017;23:3529-36.
6. Pheneger T, et al. Cancer Research 2009;69:1795.

TKI: tyrosine kinase inhibitor

Improved OS and TT new brain lesion for patients w/ Tucatinib

Figure 2. Efficacy of Tucatinib Combination Therapy in Patients With Brain Metastases

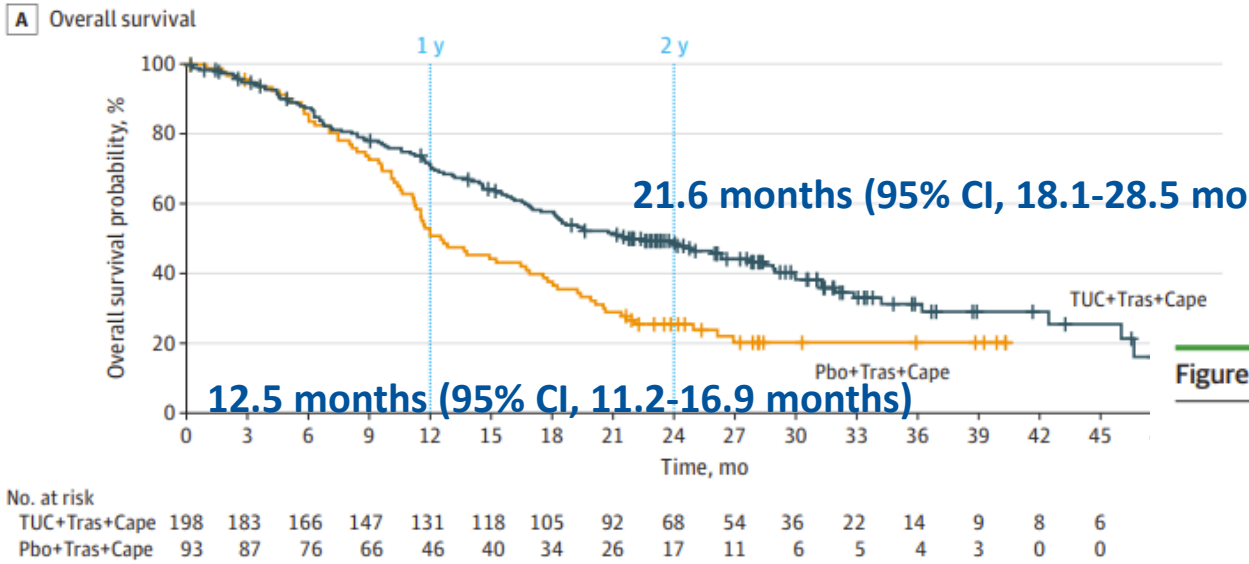
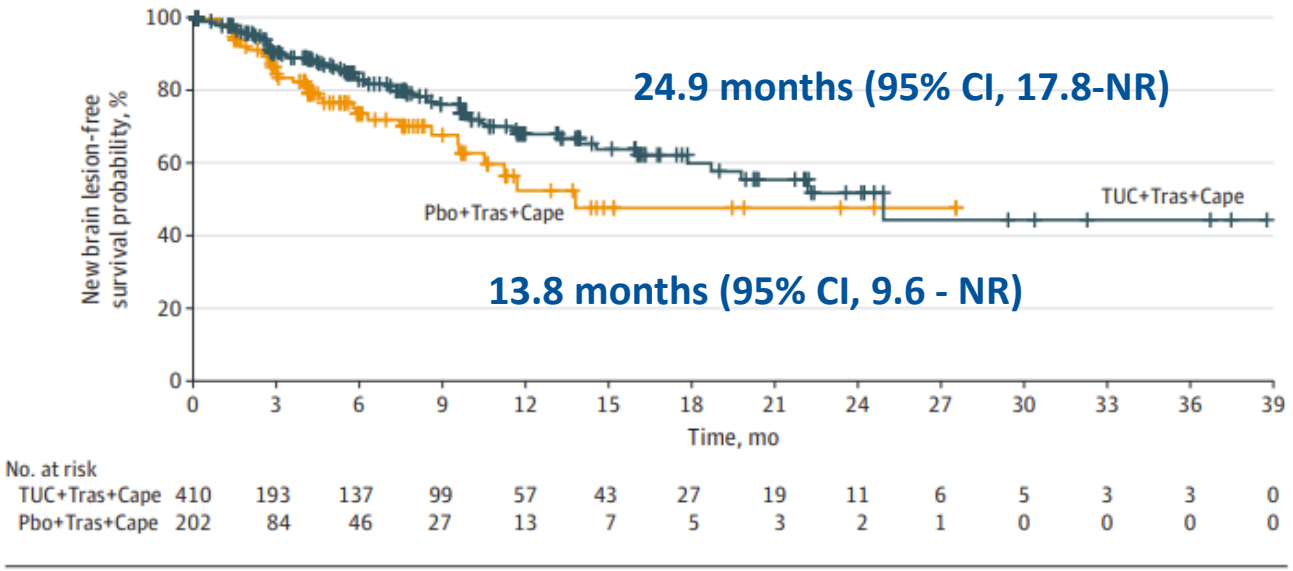


Figure 3. New Brain Lesion–Free Survival According to Investigator Assessment for All Patients



Lin N….Anders, CK…et. al. Jama Oncology, December 2022

Secondary Prevention Clinical Trial: BRIDGET

BRIDGET/BRE21-516: Single arm, phase II, multicenter, clinical trial of tucatinib added to trastuzumab/pertuzumab or T-DM1 in patients with isolated intracranial progression in HER2+ advanced breast cancer

- Advanced HER2+ BC
- Adjuvant or Metastatic HP/T-DM1
- Stable extracranial disease
- 1st or 2nd intracranial event

ER+/HER2+ disease allowed, endocrine therapy can continue

N=50

Local therapy with stereotactic radiosurgery +/- surgical resection if indicated

Tras/pertuz + tucatinib

T-DM1 + tucatinib

Staging q9 weeks: MRI brain, systemic

Intracranial Progression

PI: Sarah Sammons, MD
Co-PI: Carey K. Anders
Coordinated through HCRN

Extracranial Progression

Tucatinib

Tras/pertuz → T-DM1 → Tras/Capecitabibe

If intracranial disease stable with extracranial progression, continue tucatinib into next line

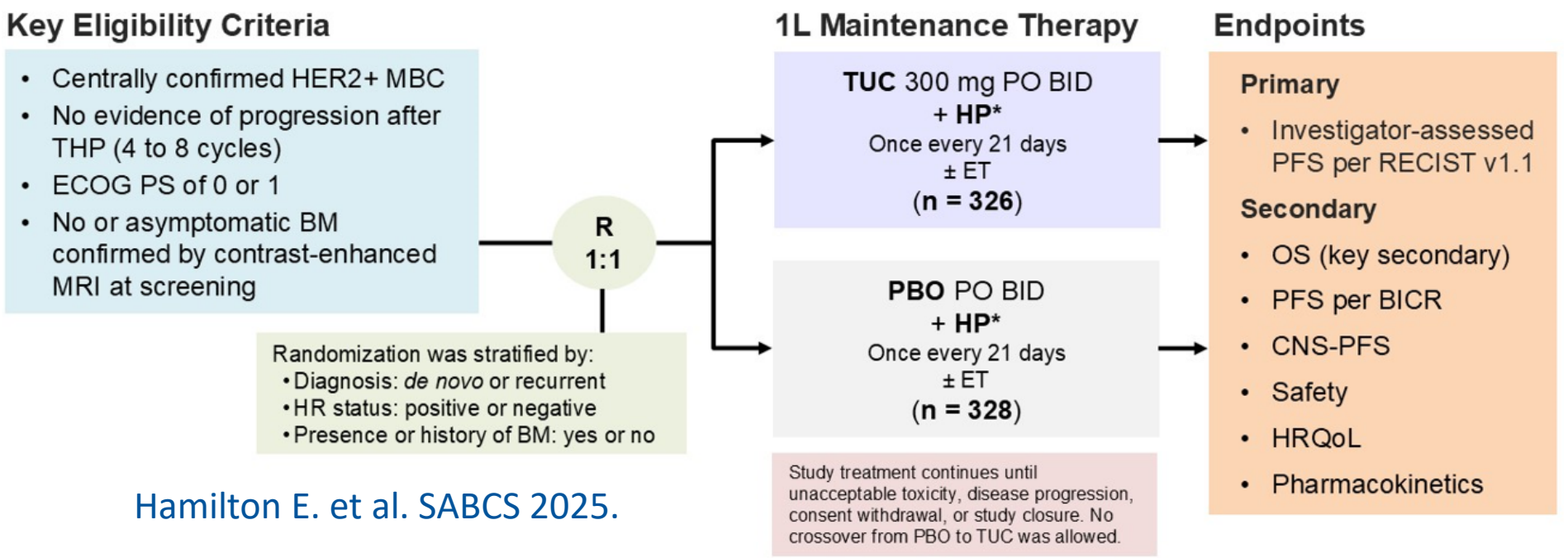
Clinical Trials.gov
NCT05323955

Primary objective: Intracranial PFS (RANO-BM)
Secondary objectives: PFS, 2nd intracranial PFS, OS, CBR, PROs, safety, time to next line therapy

Efficacy of Tucatinib/HP maintenance in HER2+ MBC

HER2CLIMB-05 Design

HER2CLIMB-05 is a randomized, double-blind, placebo-controlled, international, phase 3 trial (NCT05132582)

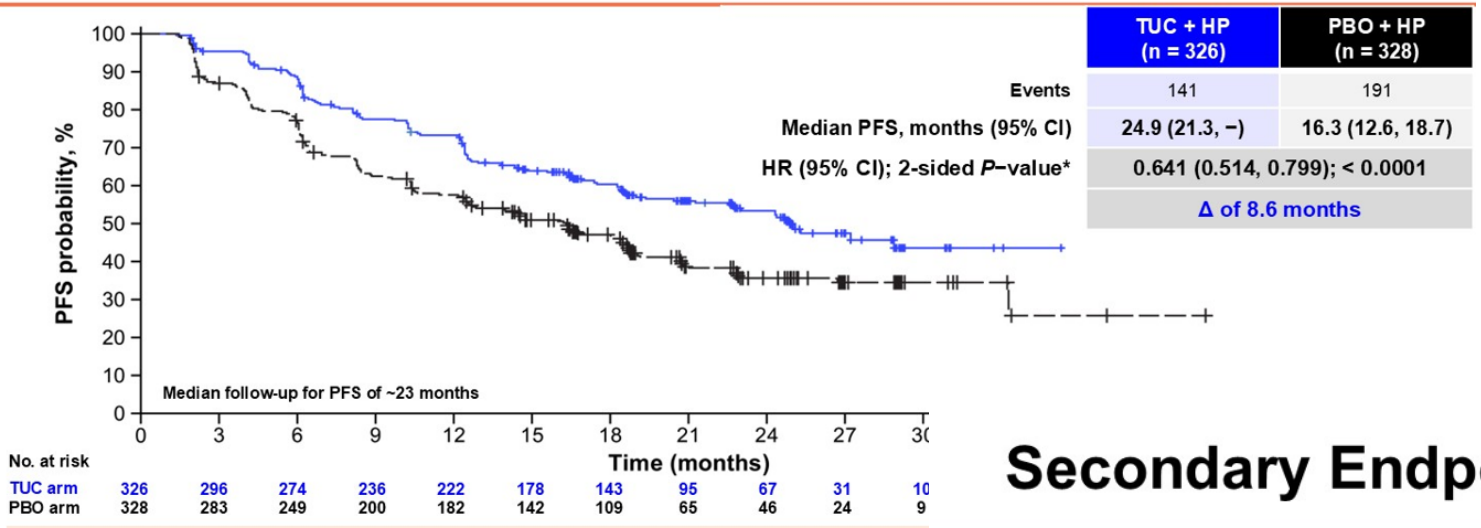


Hamilton E. et al. SABCS 2025.

N = 654 patients randomized, of which n ~ 40 pts (~12%) in each Arm had a h/o brain metastases

Efficacy of Tucatinib/HP maintenance in HER2+ MBC

Primary Endpoint: Investigator-Assessed PFS



	TUC + HP (n = 326)	PBO + HP (n = 328)
Events	141	191
Median PFS, months (95% CI)	24.9 (21.3, –)	16.3 (12.6, 18.7)
HR (95% CI); 2-sided *P*–value*	0.641 (0.514, 0.799); < 0.0001	
	Δ of 8.6 months	

Addition of TUC to 1L maintenance therapy extended m
in patients with HER2+ MBC, an **8.6-month** improvement c

Overall improvements in PFS
-- Tucatinib 24.9 months
-- Placebo 16.3 months

Hamilton E. et al. SABCS 2025.

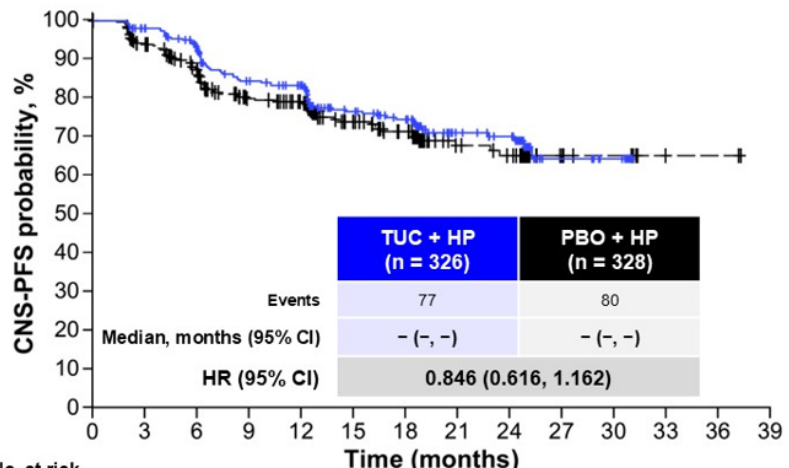
Secondary Endpoint: CNS-PFS

NO difference in CNS-PFS in ITT

Improved in CNS PFS for those with BM's
-- Tucatinib 8.5 months
-- Placebo 4.3 months

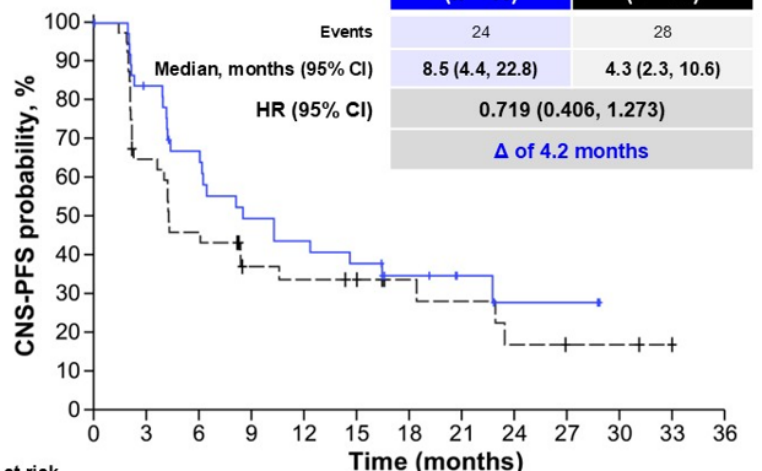
Consistent with improvement in time to New brain lesion in Her2Climb……

ITT population



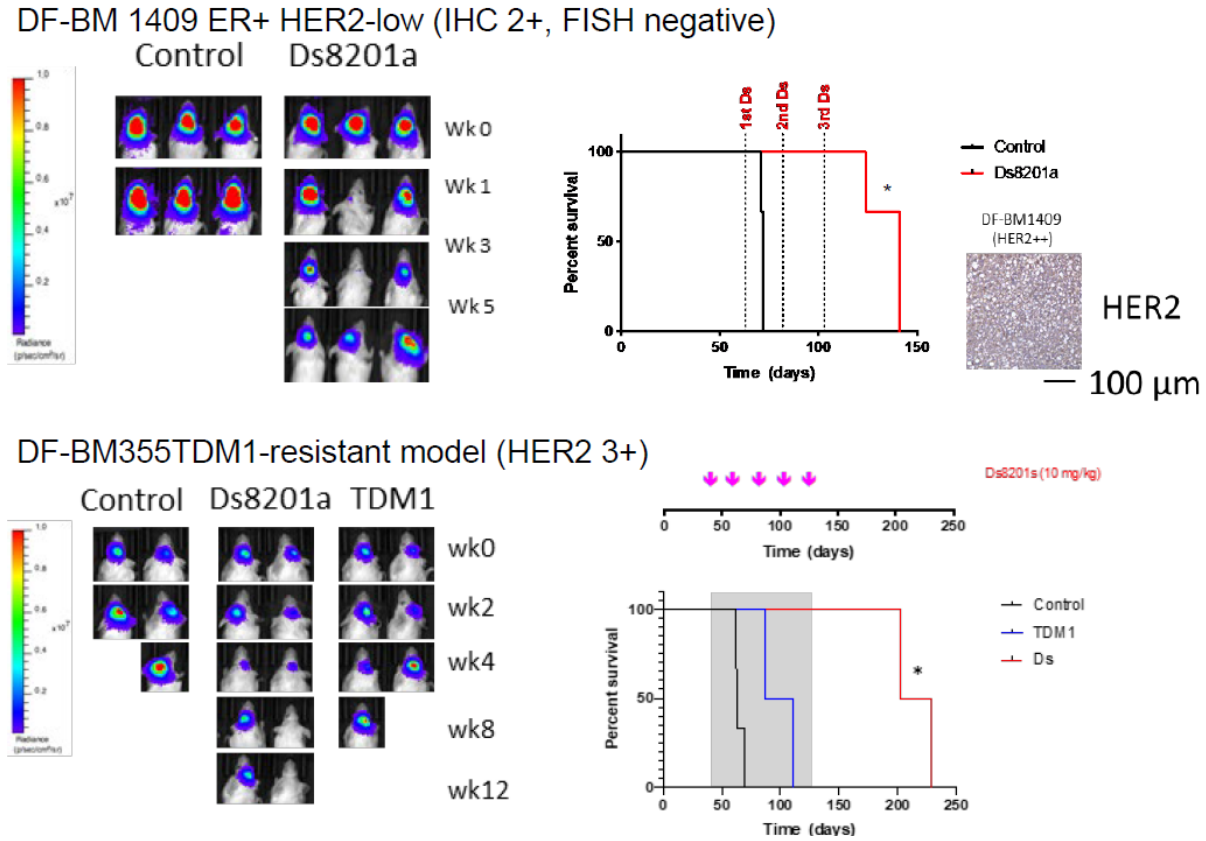
	TUC + HP (n = 326)	PBO + HP (n = 328)
Events	77	80
Median, months (95% CI)	– (–, –)	– (–, –)
HR (95% CI)	0.846 (0.616, 1.162)	

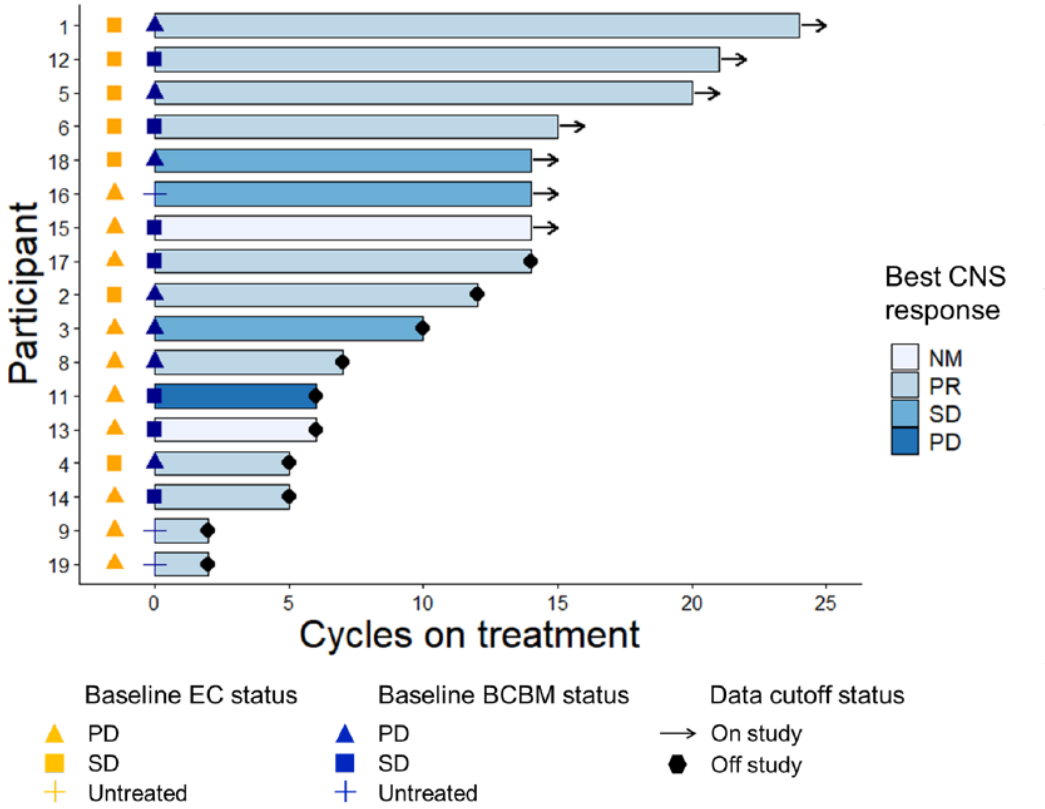
Exploratory analysis: Patients with baseline BM



	TUC + HP (n = 41)	PBO + HP (n = 40)
Events	24	28
Median, months (95% CI)	8.5 (4.4, 22.8)	4.3 (2.3, 10.6)
HR (95% CI)	0.719 (0.406, 1.273)	
	Δ of 4.2 months	

TDxd in Her2+ *Active* Breast Cancer Brain Metastases





Additional modeling illustrates efficacy of TDxD in Her2+brain Metastases murine (PDX) models – both ER+ and ER -

17 participants with active brain mets (median 14 mos since radiation therapy): iORR 73% (11/15 with measureable dz

Dana-Farber Cancer Institute

Duke Cancer Institute

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Kabraji et al. CCR. 2022.

Study	Retro/Pro	n	CNS Status(es)	CNS-ORR	OS/PFS
Kabraji et al. CCR 2023	Retrospective	n=15 evaluable	Stable or Active (Untreated or Progressive) HER2+ BrM	73% (0% CR + 73% PR)	CNS-PFS @ 12 mos PFS: 74.7% mPFS @ 12 mos: 57.8%
TUXEDO (*Bartsch et al. Nat Med 2022*)	Prospective	n=15	Newly diagnosed untreated or Progressive HER2+ BrM	73.3% (13% CR + 60% PR)	mOS: Not reached mPFS: 14 mos
DESTINY-01/02/03 (*Hurvitz et al. ESMO 2023*)	Prospective (pooled)	n=85	Treated/Stable or Untreated/Active HER2+ BrM	70-80%	CNS PFS: 12.3 mos (Stable); 18.5 mos (Active)
DESTINY-12 (*Lin N et al. ESMO, 2024*)	Prospective	n=263	Stable or Active (Untreated or Progressive) HER2+ BrM	71.7% (All) (79.2% Stable; 62.3% Active	

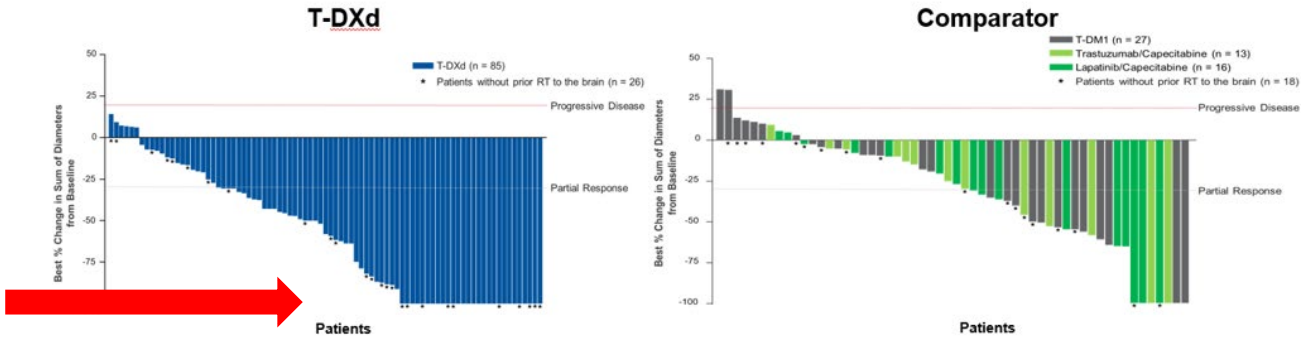
T-DXd Clinical Performance in HER2+ Breast Cancer Brain Metastases

iORR ~70% across studies

Including CR's

DESTINY-Breast01, -02, and -03 — *Hurvitz et al. ESMO 2023.*

Best Percentage Change from Baseline in Sum of Diameters of Brain Tumors



- The shrinkage of BMs in response to T-DXd was more prominent, whereas in the comparator pool, BMs showed less of a response

Trastuzumab Deruxtecan in *First Line* Her2+ MBC

DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)[1,2]

Patient population
- 1L HER2+ a/mBC
- DFI >6 mo from last (neo)adjuvant therapy
- One prior line of ET for a/mBC permitted
- Asymptomatic BMs allowed

R 1:1:1

- n=387 → T-DXd† + placebo — *Arm blinded until final PFS analysis*
- n=383 → T-DXd† + pertuzumab‡
- n=387 → THP — Taxane§ + trastuzumab¶ + pertuzumab‡

Endpoints

Primary
- PFS (BICR)

Key secondary
- OS

Secondary
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerab

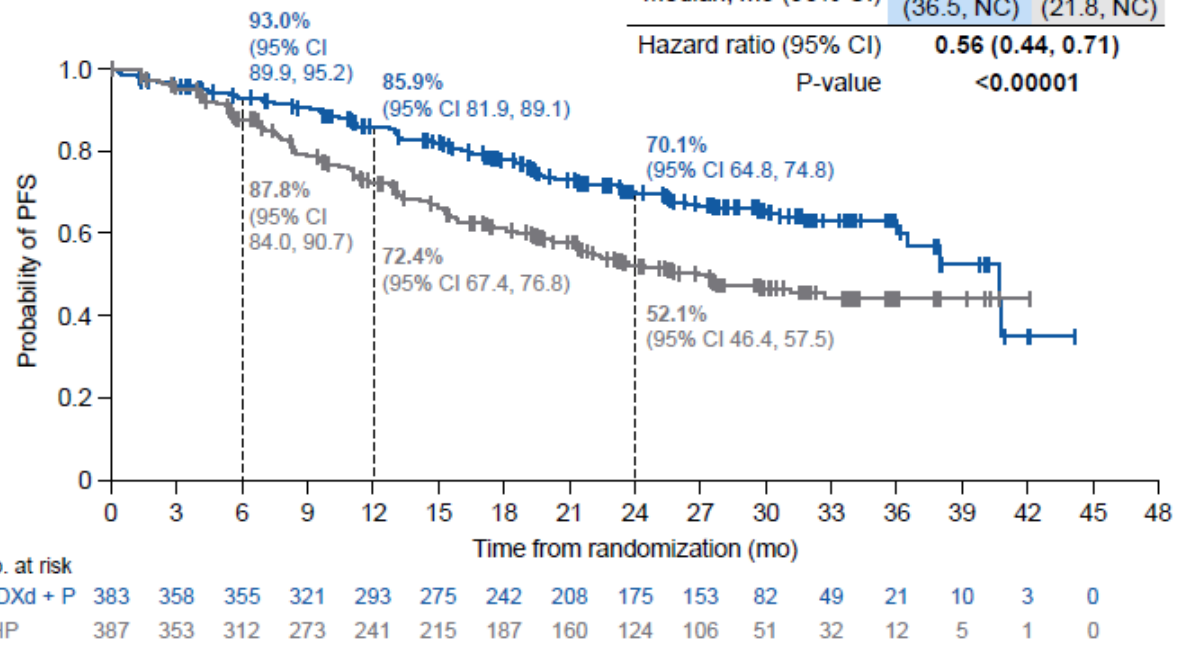
Stratification factors
- **De-novo (~52%) vs recurrent a/mBC**
- **HR+ (~54%) or HR−**
- ***PIK3CA*m detected (~31%) vs not detected**

- If T-DXd was discontinued owing to AEs (except Grade >2 ILD), switch to trastuzumab‖
- Concurrent use of ET (aromatase inhibitor or tamoxifen) was all with HR+ disease after six cycles of T-DXd or discontinuation o

Tolaney et al. ASCO 2025.
Loibl et al. ESMO 2025

DESTINY-Breast09 interim analysis (DCO February 26, 2025)
PFS by BICR: primary endpoint[1]

	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7 (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001	



T-DXd plus Pertuzumab may be used in first line in some patients;
DB11 and DB05 illustrate activity in neoadjuvant and adjuvant setting respectively. Impact on later line treatments?

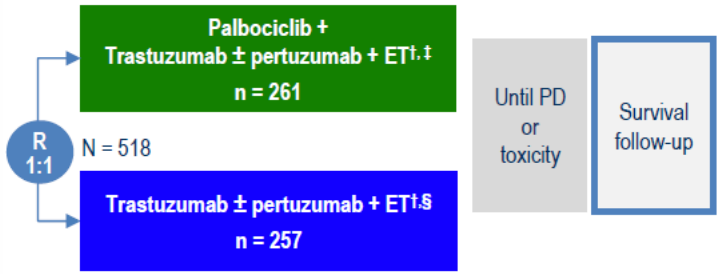
Prevention of CNS Metastases in ER+/Her2+MBC

PATINA: Randomized, Open-Label, Phase III Trial (AFT-38)[1,2]*

Objective: To evaluate the addition of palbociclib to anti-HER2 and ET for patients with HR+/HER2+ breast cancer

REGISTRATION
- Histologically confirmed HR+/HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6–8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

KEY ELIGIBILITY CRITERIA
- Completion of induction chemotherapy and no evidence of disease progression (ie, CR, PR, or SD)
- Patients with a history or presence of asymptomatic CNS metastases were eligible



Primary Outcome
- Investigator-assessed PFS

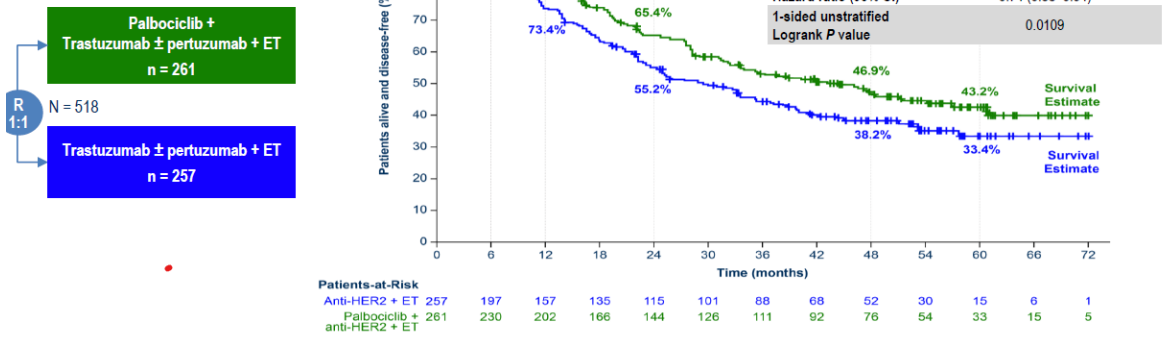
Secondary Outcomes
- OS
- 3- and 5-year survival probabilities
- ORR / DOR / CBR
- Safety
- PRO
- Incidence of CNS metastases

Lower incidence of CNS Metastases
At 36 months:

-- 13.8% for Palbo + ET + HP
-- 20.4% for ET + HP

Similar results for those with CNS mets
At baseline (Metzger et al. SABCS 2025)

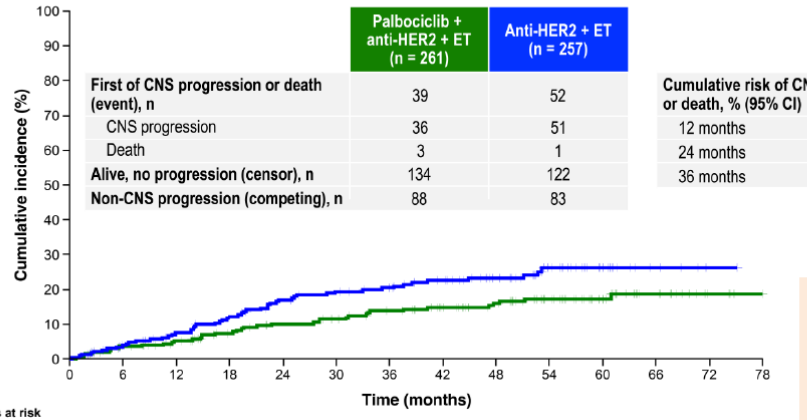
PATINA Primary Endpoint: Investigator-Assessed PFS[1]



	Palbociclib + anti-HER2 + ET	Anti-HER2 + ET
Events	127/261	135/257
Median PFS (95% CI), months	44.3 (32.4–56.8)	29.1 (23.3–38.6)
Hazard ratio (95% CI)	0.74 (0.58–0.94)	
1-sided unstratified Logrank *P* value	0.0109	

Cumulative Incidence of CNS Progression[a] or Death

All Randomized Patients



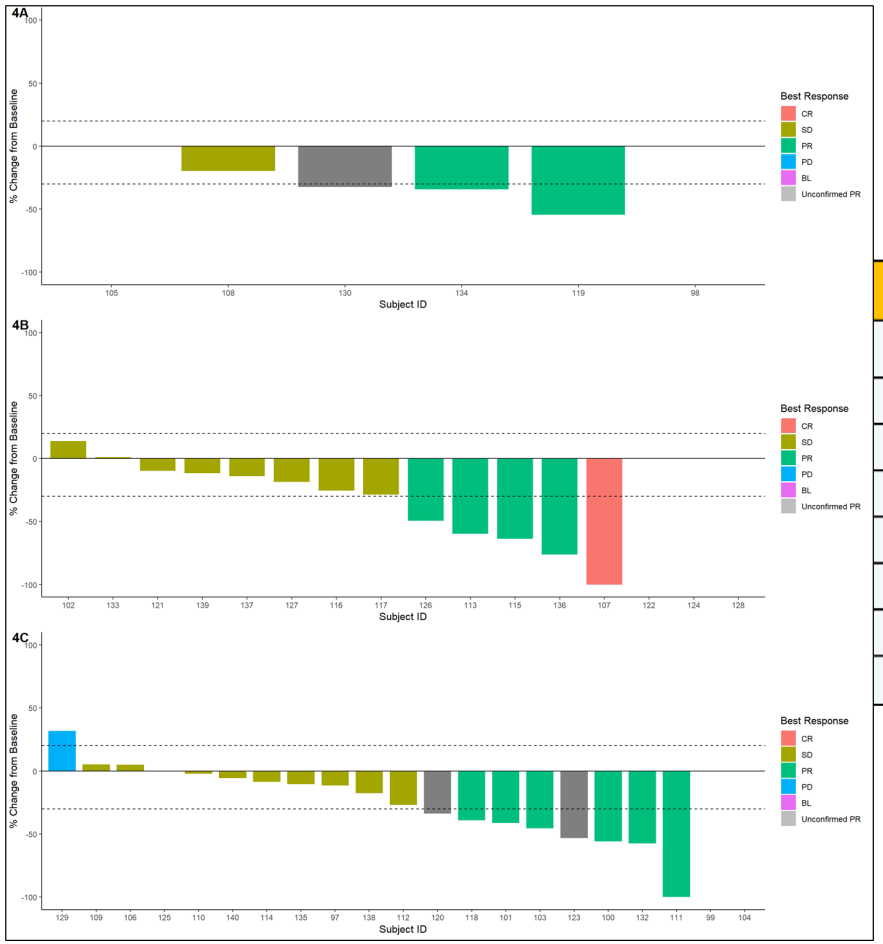
	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
First of CNS progression or death (event), n	39	52
CNS progression	36	51
Death	3	1
Alive, no progression (censor), n	134	122
Non-CNS progression (competing), n	88	83

	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
Cumulative risk of CNS progression or death, % (95% CI)		
12 months	5.2 (2.9–8.5)	7.5 (4.6–11.5)
24 months	10.1 (6.7–14.3)	17.0 (12.3–22.3)
36 months	13.8 (9.7–18.6)	20.4 (15.3–26.1)

- At 36 months, the cumulative incidence of CNS progression or death was 13.8% vs 20.4% for palbociclib vs control (Gray's test *P* = 0.0404).

TBCRC 022: Neratinib and Trastuzumab-Emtansine (T-DM1) for HER2+ BCBM

Figure 2. Waterfall Plot- % CNS Response



Notably, maximum dose of neratinib with TDM1 was 160mg daily

4A: Untreated **4B: No prior TDM1** **4C: Prior TDM1**

Table 2. Best RANO-BM CNS Response

Response	Cohort 4A	Cohort 4B	Cohort 4C
CR	0 (0)	1 (5.9)	0 (0)
PR	2 (33.3)	4 (23.5)	6 (28.6)
Unconfirmed PR	1 (16.7)	0 (0)	2 (9.5)
SD	2 (33.3)	8 (47.1)	10 (47.6)
PD	0 (0)	0 (0)	1 (4.8)
Unavailable (off tx before imaging)	1 (16.7)	3 (17.6)	2 (9.5)
CNS ORR	**33.3% (4.3-77.7%)**	**29.4% (10.3-56.0%)**	**28.6% (11.3-52.2%)**
CNS CR + PR + SD ≥6 mos	50% (11.8-88.2%)	35.3% (14.2-61.7%)	33.3 (14.6-57.0%)

Diarrhea AE, despite prophylaxis
Grade 2: 14/44 patients
Grade 3: 10/44 patients

Freedman RA et al SABCS, 2022.
Freedman RA et al Annals of Onc 2024.

PATRICIA: High dose trastuzumab with pertuzumab for Her2+ BCBM

Pertuzumab plus high-dose trastuzumab for HER2-positive breast cancer with brain metastases: PATRICIA final efficacy data

N = 39 pts

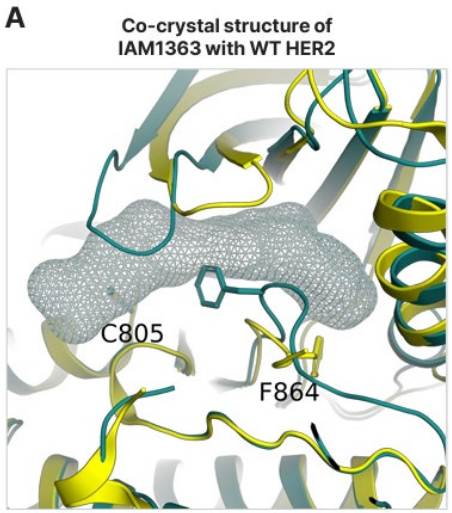
Nancy U. Lin[1,8], Priya Kumthekar[2,8], Solmaz Sahebjam[3,7], Nuhad Ibrahim[4], Anita Fung[5], Anna Cheng[5], Alan Nicholas[5], Jesse Sussell[5] and Mark Pegram[6]

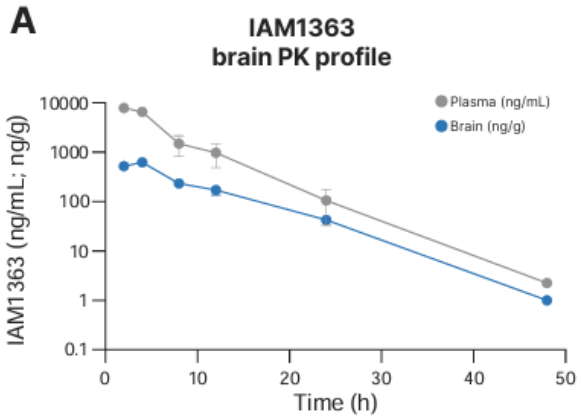
- Another option is high dose Trastuzumab (6mg/kg IV q 1 week) plus standard 3 week dosing of Pertuzumab per the PATRICIA Study
  - Intracranial ORR = 11%; CNS PFS = 4.6 months; OS = 27.2 months
  - No clinically meaningful changes in LVEF; only 1 pt discontinued therapy due to Grade 3 decline in LVEF with prior cardiac history

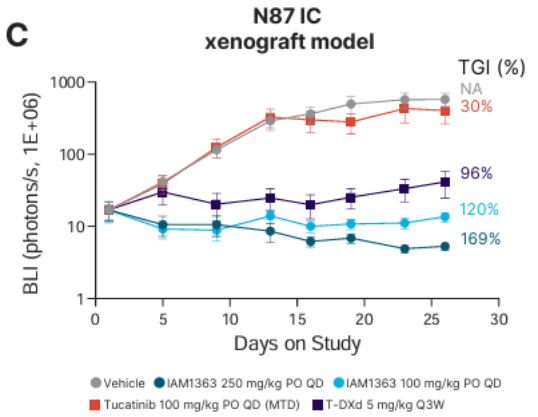
Lin et al. NPJ Breast Cancer 2023.

Next generation Her2-targeting TKI: IAM1363

NCT06253871

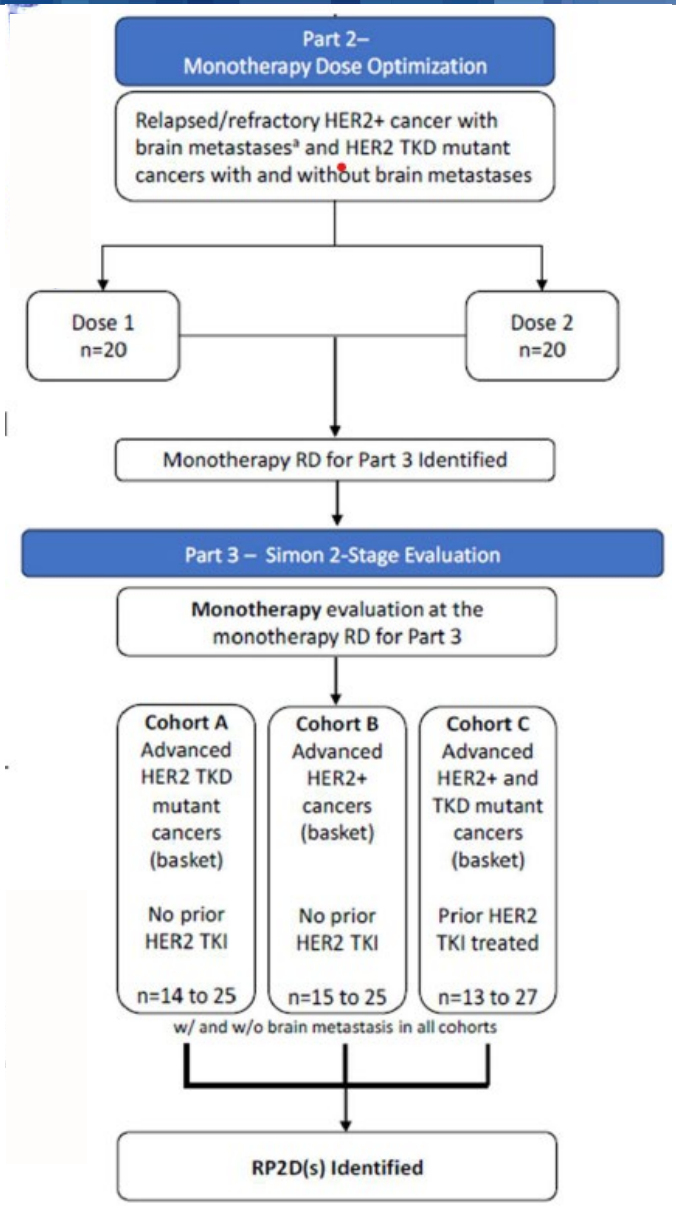






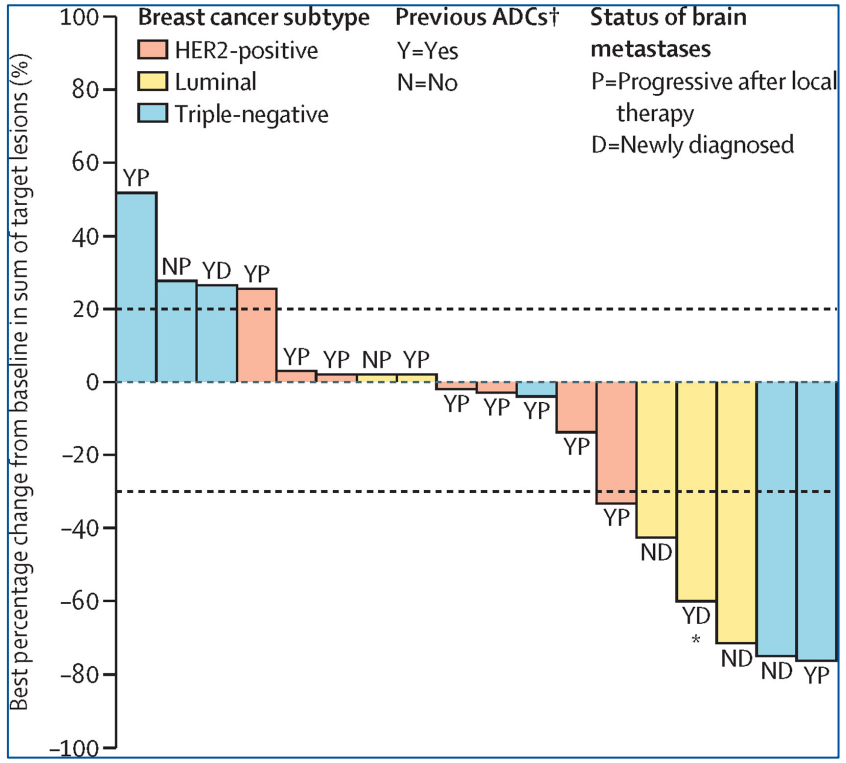
	Intracranial activity	Exon20 mutant activity	In vivo selectivity[1] Cell pHER2 vs. pEGFR[7]	In vivo selectivity[1] Biochemical HER2 vs. EGFR[8]
Tucatinib (Pfizer)	Marginal[2]	No[3]	**>1200**	-
Zongertinib (BI)	No[4]	**Yes**	-	20
ZN-1041 (Zion/Roche)[5]	**Yes**	No[6]	-	-
ELVN-002[5]	Moderate	**Yes**	180[9]	47[9]
NVL-330[5]	**Yes**	**Yes**	96[9,10]	-
IAM1363	**Yes**	**Yes**	**2800**	**5200**

Kulyk L. et al. AACR 2024.



TUXEDO-3: Patritumab deruxtecan (HER3-DXd) in T-DXd Pretreated HER2+ BrMs

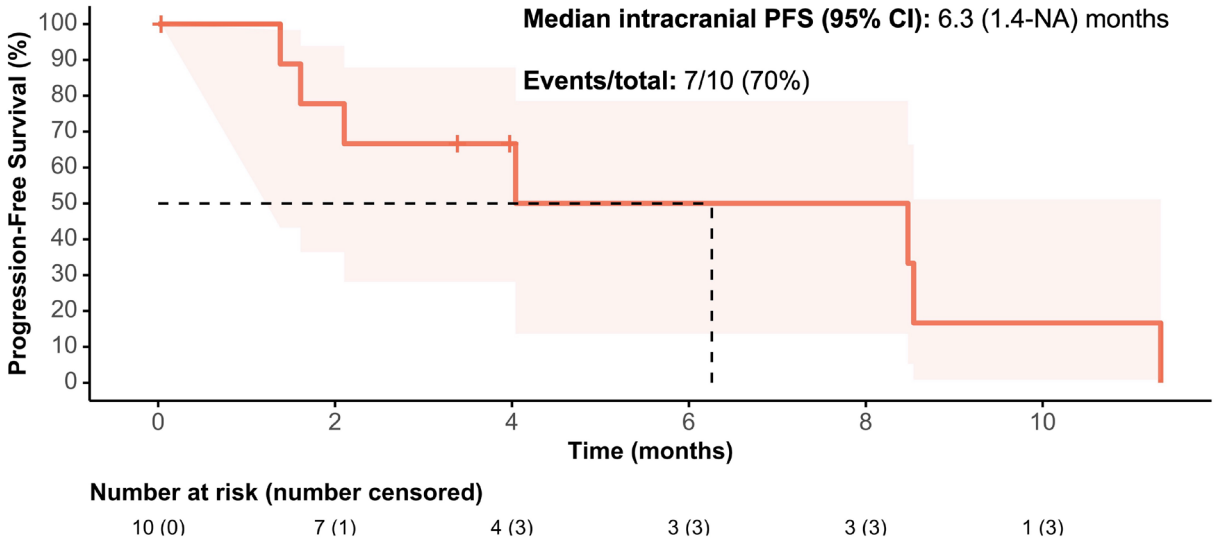
Slide courtesy of Sarah Sammons, MD



21 pts MBC (all subtypes), active CNS

Intracranial ORR 23·8%, (95% CI 8·2–47·1)

Bartsch, Lancet 2025



Bartsch, SABCS 2025

The challenge of Her2+ Leptomeningeal Disease

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Leptomeningeal Metastases

LEPTOMENINGEAL METASTASES: SYSTEM

- Treatment
  - Systemic therapy specific to primary cancer type; emphasizing drugs with good CNS penetration
  - Intra-CSF therapy[1]
    - Other Recommended
      - Temozolomide[2]
      - Thiotepa[3]
      - Topotecan[4]
      - Etoposide[5]
      - Cytarabine[6-9]
      - Methotrexate[8,10-12]
  - Lymphoma
    - Intra-CSF therapy
      - Rituximab[7]
    - High-dose methotrexate[b,13]
  - Breast cancer
    - Preferred
      - Fam-trastuzumab deruxtecan-nxki[14]
    - Other Recommended
      - Intra-CSF therapy
        - Methotrexate[8,10,11]
        - Trastuzumab[a] (HER2 positive)[15]
    - Useful in Certain Circumstances
      - High-dose methotrexate[b,16,17,18]

ARTICLES
https://doi.org/10.1038/s41591-022-01935-8
nature medicine

Check for updates

OPEN

Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial (TUXEDO TRIAL); n = 15pts

Rupert Bartsch[1], Anna Sophie Berghoff[1], Julia Furtner[2], Maximilian Marhold[1],

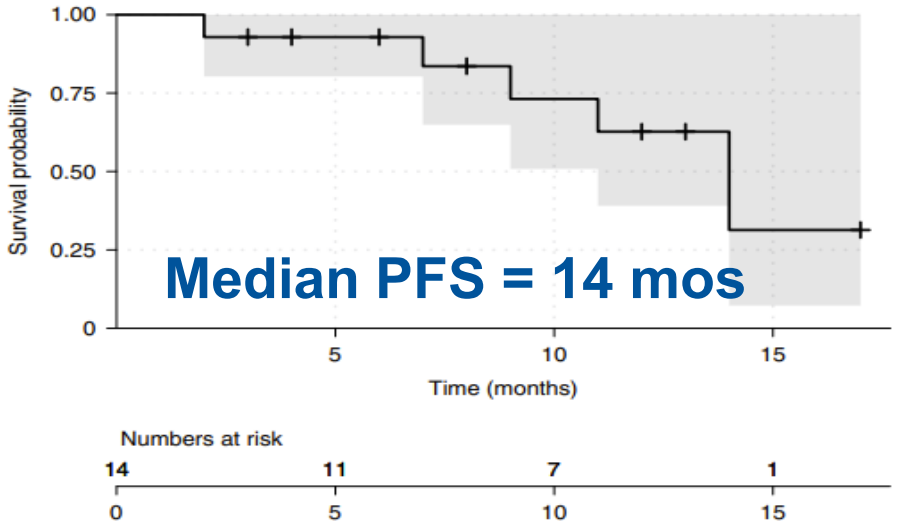


Fig. 3 | Kaplan–Meier plot showing progression-free survival times (months) in the TUXEDO-1 trial.

iORR = 73%
iCR = 13%, iPR = 60%

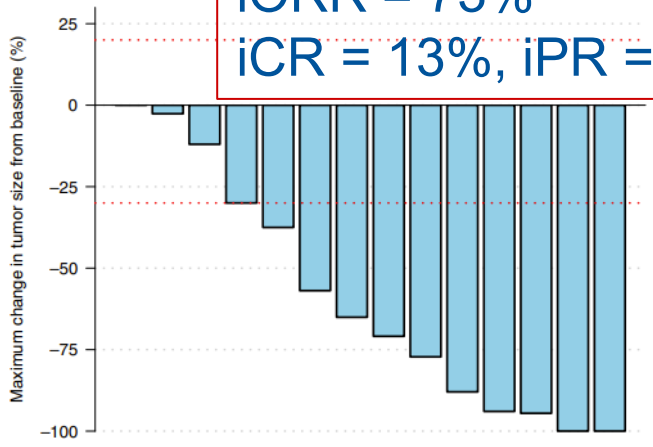


Fig. 2 | Waterfall plot of responses in patients evaluable for response by RANO-BM criteria in the TUXEDO-1 trial. Blue bars illustrate the radiographic change of maximum brain metastasis size after start of trastuzumab deruxtecan therapy compared to the baseline measurement. Red dotted lines denote thresholds for response and progression by RANO-BM criteria.

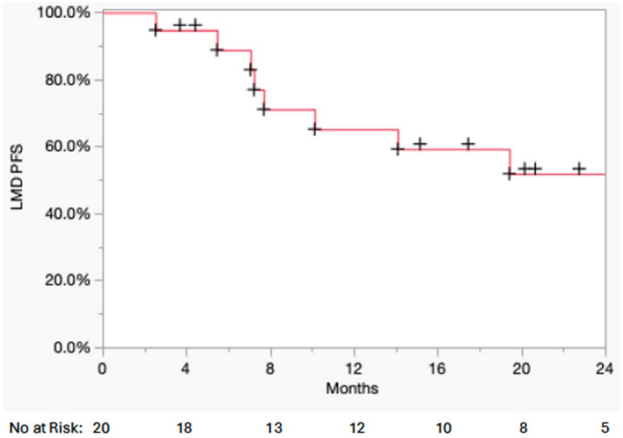
Intrathecal Trastuzumab +/- Pertuzumab for HER2+ LMDz

Historical Controls IT trastuzumab

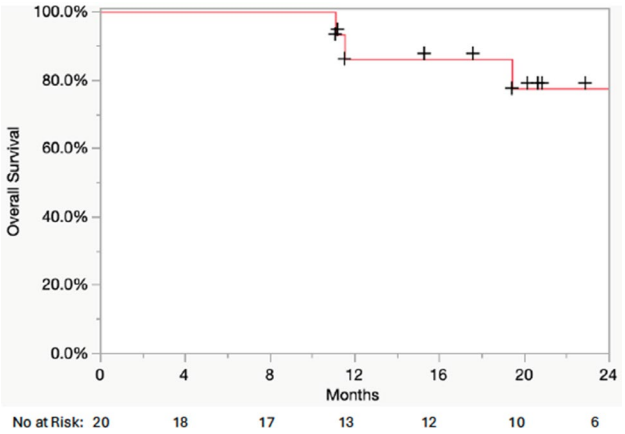
Intra-CSF Trastuzumab in pretreated HER2+ MBC			
Name	Treatment	N	Results
Zagouri et al	Meta analysis of case series	N= 58	CNS-PFS= 5.2months OS= 13.2 mo
Kumthekar et al 2022	Phase I/II Trastuzumab IT 80mg Twice week	N= 26	PFS= 2.8 mo OS= 10.5 mo
Oberkampf et al 2023	Phase II Trastuzumab IT 150mg once a week	N= 19	LM-PFS = 5.9 mo OS = 7.9 mo

Slide courtesy of Sarah Sammons, MD

Phase II IT Tras/Pertuzumab Post-RT, mostly WBRT (n = 20)



12m LM-PFS
65%
Median MR



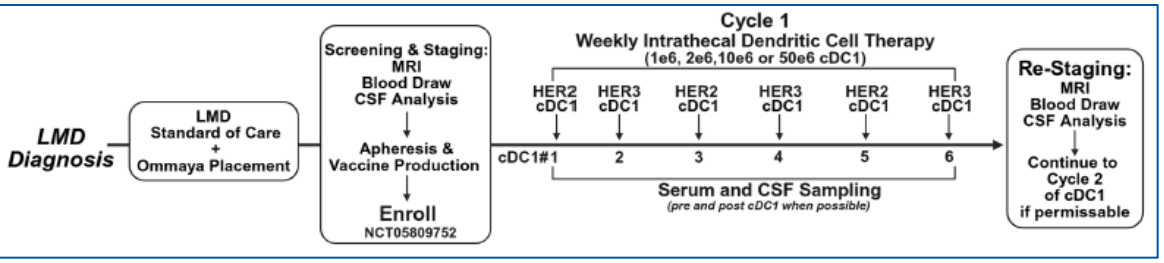
12m OS
86%
Median MR

What concurrent Therapies?
Prior Therapies?

Ahmed K et al SABCS 2025.

Novel Intrathecal LMD Strategies to Watch

IT Dendritic Cell Therapy



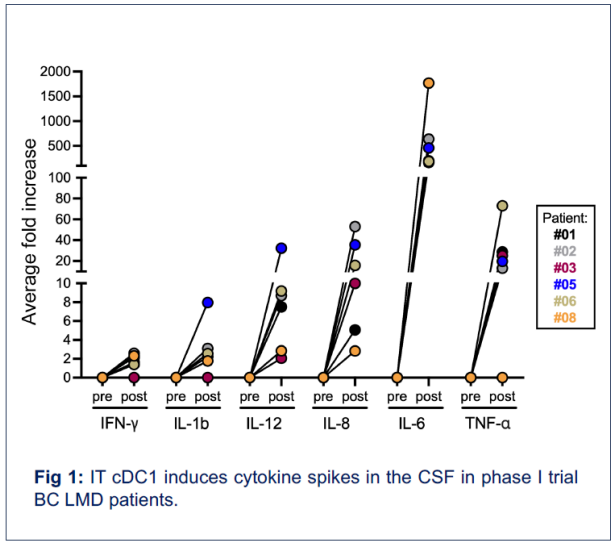


Fig 1: IT cDC1 induces cytokine spikes in the CSF in phase I trial BC LMD patients.

N=6 pts
TNBC and HER2+
Robust CSF immune response

Antibody formation

4/6 PD within 18 wks.

Forsyth, P. et al SABCS 2025.

Slide courtesy of Sarah Sammons, MD

IT HP + Radiation

Phase 1 dose escalation:

IT Tras 80 mg, RP2D IT Pertuzumab 80 mg

4 weeks twice-weekly, weekly in cycle 2, and every 2 weeks thereafter

Ahmed K., Lancet Oncol 2024

Table. Patient and Treatment Characteristics

Patient No.	Age, y	KPS score	LMD diagnosis	Concurrent systemic treatment	Pertuzumab dose, mg	Receptor	Radiation administered	Adverse event	Best leptomeningeal response
1	40s	70	CSF and radiographic findings	Trastuzumab plus pertuzumab	10	HR⁺/ERBB2⁺	Whole brain	NA	PR
2	50s	90	Radiographic findings	Trastuzumab plus pertuzumab	20	HR⁻/ERBB2⁺	Prior whole brain and SRS	Grade 1 headache	Stable disease
3	50s	80	CSF and radiographic findings	Sacituzumab govitecan	40	HR⁻/ERBB2⁺	Whole brain	Grade 2 fatigue	Stable disease
4	40s	60	CSF and radiographic findings	Trastuzumab plus pertuzumab	80	HR⁻/ERBB2⁺	Whole brain	Grade 1 arthralgia and extremity pain	CR
5	50s	90	Radiographic findings	Trastuzumab deruxtecan	80	HR⁻/ERBB2⁺	Prior whole brain	Grade 1 fatigue and headache	PR
6	40s	90	Radiographic findings	Trastuzumab	80	HR⁻/ERBB2⁺	Prior whole brain and FSRS	Grade 1 fatigue and nausea	Stable disease
7	60s	80	Radiographic findings	Trastuzumab deruxtecan	80	HR⁻/ERBB2⁺	FSRS	Grade 1 paresthesia	CR
8	30s	90	Radiographic findings	Trastuzumab	80	HR⁺/ERBB2⁺	Whole brain	NA	PR
9	50s	90	Radiographic findings	Trastuzumab plus pertuzumab	80	HR⁻/ERBB2⁺	Prior whole brain, SRS, and spine RT	NA	Stable disease

Abbreviations: CR, complete response; CSF, cerebrospinal fluid; ERBB2, erb-b2 receptor tyrosine kinase 2 (formerly HER2); FSRS, fractionated stereotactic radiosurgery; HR, hormone receptor; KPS, Karnofsky Performance Status; LMD, leptomeningeal disease; NA, not applicable; PR, partial response; RT, radiation therapy; SRS, stereotactic radiosurgery.

Conclusions and New Directions

- Systemic therapies for Her2+ BCBM are evolving
  - Her2-targeting TKI's and ADC's are the mainstay
  - Additional targets are emerging (i.e. CDK4/6i, HER3, etc.)
- Intrathecal therapies for HER2+ LMDz is re-emerging
  - Inclusive of Her2/3 targeting, as well as immunotherapy strategies
- Continued emphasis on clinical trial participation to advance the field for our patients!

Thanks and Questions!