



# Current and Evolving Approaches for HER2+ Breast Cancer Brain Metastases

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**DukeHealth**



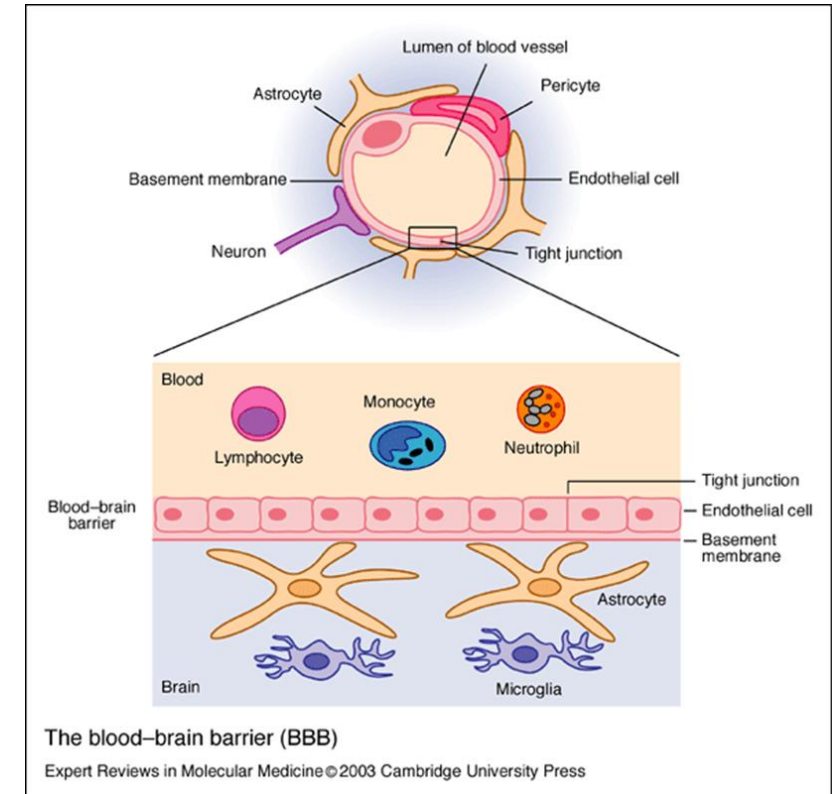
# Disclosures

- Research funding PUMA, Lilly, Merck, Seattle Genetics, Nektar, Tesaro, G1-Therapeutics, ZION, Novartis, Pfizer, Astra Zeneca, Elucida, Caris, Incyclix, Beigene
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- Royalties: UpToDate, Jones and Bartlett



# Breast Cancer Brain Metastases: Challenges Faced

- Devastating, feared and increasingly common consequence of breast cancer
  - Incidence 30% HER2+<sup>1</sup>, 50% triple negative<sup>2</sup> 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



<sup>1</sup> Bendell et al. Cancer 2003, <sup>2</sup> Lin et al. Cancer 2008



# NCCN: Systemic Therapy Options expanded in 2025 - 2026



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## NCCN Guidelines Version 3.2025 Brain Metastases

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### BRAIN METASTASES<sup>a</sup>: SYSTEMIC THERAPY<sup>b</sup>

#### • Tumor Agnostic<sup>b</sup>

##### ▶ NTRK gene fusion tumors

###### ◊ Preferred

- Larotrectinib<sup>1</sup>
- Entrectinib<sup>2</sup>
- Repotrectinib<sup>3</sup>

###### ◊ Other Recommended

- Temozolomide 5/28 Schedule

##### ▶ MSI-H/dMMR or TMB-H (≥10 mut/Mb) tumors for isolated brain metastases

###### ◊ Preferred

- Pembrolizumab (category 2B)<sup>c,4,5</sup>

#### • Breast Cancer<sup>a</sup>

##### ▶ HER2 positive

###### ◊ Preferred

- Tucatinib + trastuzumab + capecitabine (category 1) if previously treated with ≥1 regimen<sup>6</sup>
- Fam-trastuzumab deruxtecan-nxki if previously treated with ≥1 regimen<sup>7,8</sup>
- ◊ Other Recommended
  - Ado-trastuzumab emtansine (T-DM1)<sup>9</sup>
  - Neratinib and T-DM1<sup>10</sup>
  - Capecitabine + lapatinib<sup>11,12</sup>
  - Capecitabine + neratinib<sup>13,14</sup>
  - Pertuzumab and high-dose trastuzumab<sup>e,15</sup>
  - Paclitaxel + neratinib (category 2B)<sup>16</sup>

##### ▶ HER2 non-specific

###### ◊ Other Recommended

- Capecitabine<sup>17-21</sup>
- Cisplatin (category 2B)<sup>22,23</sup>
- Etoposide (category 2B)<sup>22,23</sup>
- Cisplatin + etoposide (category 2B)<sup>23,24</sup>
- High-dose methotrexate (category 2B)<sup>f,25</sup>

##### ▶ HER2 low

###### ◊ Useful in Certain Circumstances

- Fam-trastuzumab deruxtecan-nxki (may also be used in patients with breast cancer that is HER2 immunohistochemistry [IHC] 1+ or 2+/in situ hybridization [ISH] negative)<sup>26,27</sup>

#### • Melanoma<sup>d</sup>

##### ▶ BRAF V600E positive

###### ◊ Preferred

- Dabrafenib<sup>28-30</sup>/trametinib<sup>31</sup>
- Vemurafenib<sup>32,33</sup>/cobimetinib<sup>9</sup> (category 2B)

##### ▶ BRAF non-specific

###### ◊ Preferred

- Ipilimumab + nivolumab<sup>h,34-36</sup>
- ◊ Other Recommended
  - Ipilimumab<sup>37</sup>
  - Nivolumab<sup>h,35</sup>
  - Pembrolizumab<sup>c,38</sup>

#### • Non-Small Cell Lung Cancer (NSCLC)<sup>d</sup>

##### ▶ KRAS G12C mutation

###### ◊ Adagrasib<sup>39,40</sup>

###### ◊ Sotorasib (category 2B)<sup>41,42</sup>

##### ▶ EGFR-sensitizing mutation positive

###### ◊ Preferred

- Osimertinib<sup>43-46</sup>
- Amivantamab-vmjw + lazertinib (for exon 19 deletion or L858R)<sup>47</sup>
- Amivantamab-vmjw + carboplatin + pemetrexed (for exon 19 deletion or L858R)<sup>48</sup>
- ◊ Other Recommended
  - Osimertinib plus platinum-pemetrexed (cisplatin or carboplatin) (category 1)<sup>49</sup>
  - Pulsatile erlotinib<sup>50-52</sup>
  - Afatinib (category 2B)<sup>53</sup>
  - Gefitinib (category 2B)<sup>54,55</sup>

##### ▶ MET exon 14 mutated

###### ◊ Other Recommended

- Capmatinib<sup>56</sup>
- Tepotinib<sup>57,58</sup>

#### ▶ RET fusion positive

###### ◊ Selpercatinib<sup>59</sup>

#### ▶ ALK rearrangement positive

###### ◊ Preferred

- Brigatinib<sup>60,61</sup>
- Lorlatinib<sup>62</sup>
- Alectinib<sup>63,64</sup>
- Ceritinib<sup>65</sup>

#### ▶ ALK rearrangement positive or ROS1 positive

###### ◊ Crizotinib (category 2B)<sup>66</sup>

#### ▶ ROS1 positive

###### ◊ Repotrectinib<sup>67</sup>

#### ▶ PD-L1 positive

###### ◊ Other Recommended

- Pembrolizumab<sup>c,38,68</sup> (tumor proportion score [TPS] ≥1%)
- Nivolumab<sup>h,69-71</sup> (TPS ≥1%)

#### • Small Cell Lung Cancer<sup>d</sup>

###### ◊ Preferred

- Tarlatamab-dlle<sup>72</sup>
- Topotecan (category 2B)

#### • Lymphoma<sup>d</sup>

###### ◊ High-dose methotrexate<sup>73</sup>

###### ◊ BTK inhibitor (eg, ibrutinib)<sup>74</sup>

#### • Renal Cell Carcinoma<sup>d</sup>

##### ▶ Cabozantinib<sup>75</sup>

##### ▶ Belzutifan (category 2B)<sup>76</sup> (for VHL-associated renal cell carcinoma [RCC])

### Strategies available:

#### HER2 TKIs:

Tucatinib

Neratinib

Pyrotinib (non-US)

#### Her2 targeting ADC's:

Trastuzumab Deruxtecan

TDM1

#### MoAb:

High-dose trastuzumab/  
pertuzumab

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

[Continued](#)



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



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

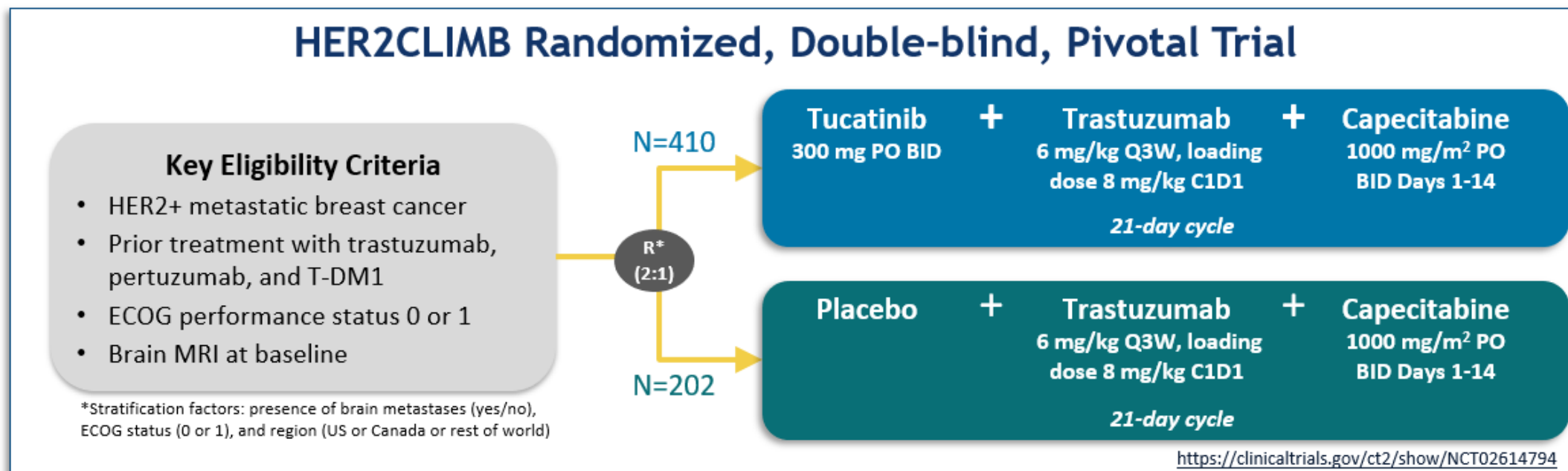
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched from their current HER2-targeted therapy regimen.
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should 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.<sup>1-4</sup>
- 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.<sup>5-6</sup>



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

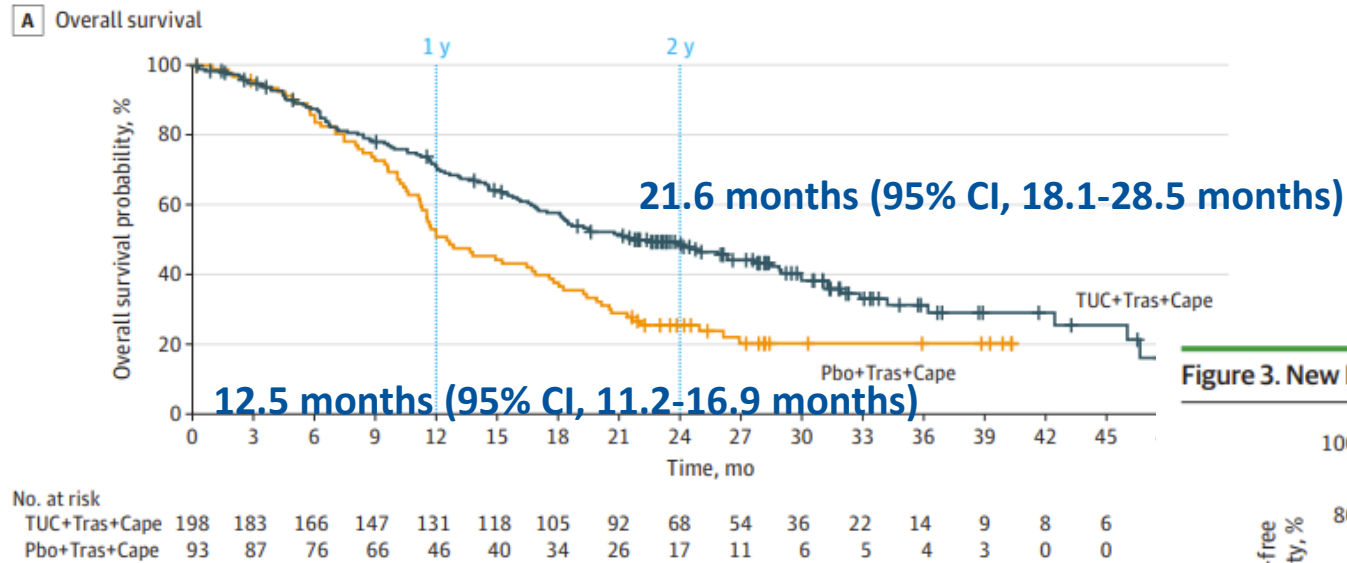
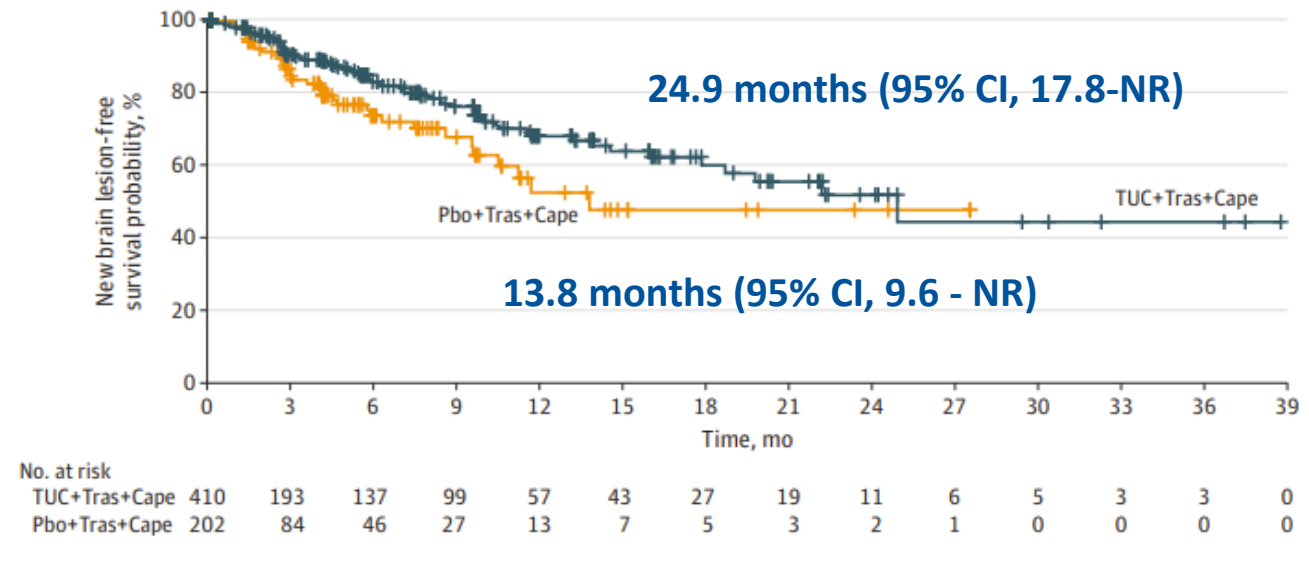


Figure 3. New Brain Lesion-Free Survival According to Investigator Assessment for All Patients





# 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
- 1<sup>st</sup> or 2<sup>nd</sup> intracranial event

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

N=50

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

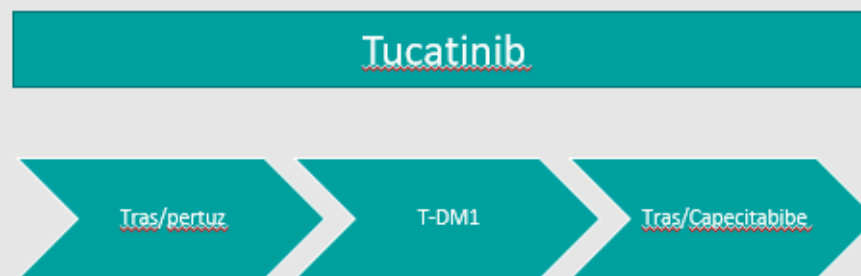
Tras/pertuz + tucatinib  
T-DM1 + tucatinib

Staging q9 weeks: MRI brain, systemic

Intracranial Progression

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

★  
Extracranial Progression



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

ClinicalTrials.gov  
NCT05323955

Primary objective: Intracranial PFS (RANO-BM)

Secondary objectives: PFS, 2<sup>nd</sup> 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)

### Key Eligibility Criteria

- Centrally confirmed HER2+ MBC
- No evidence of progression after THP (4 to 8 cycles)
- ECOG PS of 0 or 1
- No or asymptomatic BM confirmed by contrast-enhanced MRI at screening

R  
1:1

Randomization was stratified by:  
• Diagnosis: *de novo* or recurrent  
• HR status: positive or negative  
• Presence or history of BM: yes or no

### 1L Maintenance Therapy

**TUC 300 mg PO BID + HP\***  
Once every 21 days ± ET  
(n = 326)

**PBO PO BID + HP\***  
Once every 21 days ± ET  
(n = 328)

Study treatment continues until unacceptable toxicity, disease progression, consent withdrawal, or study closure. No crossover from PBO to TUC was allowed.

### Endpoints

#### Primary

- Investigator-assessed PFS per RECIST v1.1

#### Secondary

- OS (key secondary)
- PFS per BICR
- CNS-PFS
- Safety
- HRQoL
- Pharmacokinetics

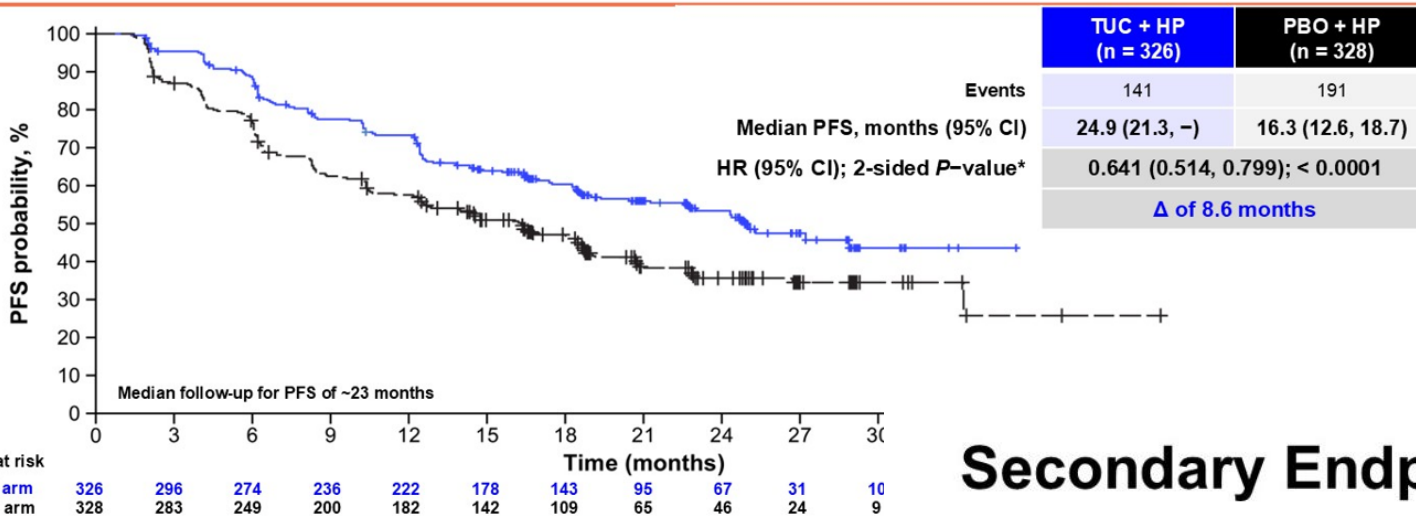
Hamilton E. et al. SABCS 2025.

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



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

Hamilton E. et al. SABCS 2025.

## Secondary Endpoint: CNS-PFS



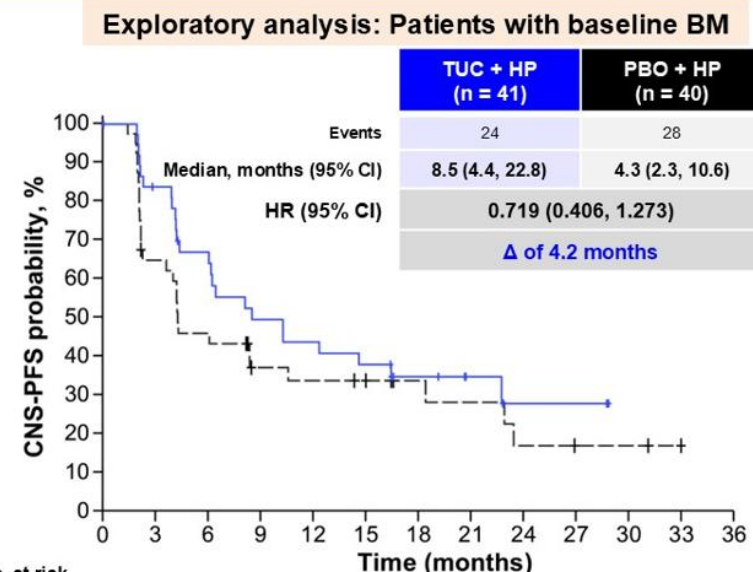
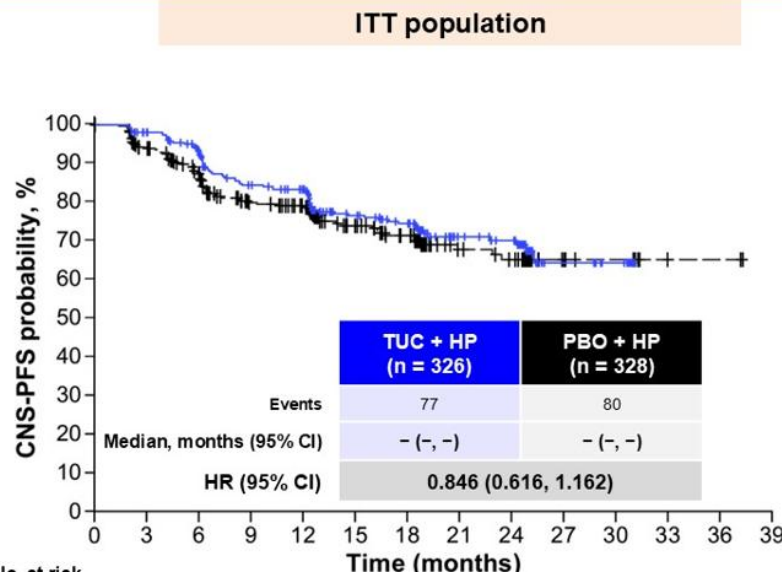
Addition of TUC to 1L maintenance therapy extended m in patients with HER2+ MBC, an **8.6-month** improvement c

**NO difference in CNS-PFS in ITT**

**Improved in CNS PFS for those with BM's**

-- Tucatinib 8.5 months  
 -- Placebo 4.3 months

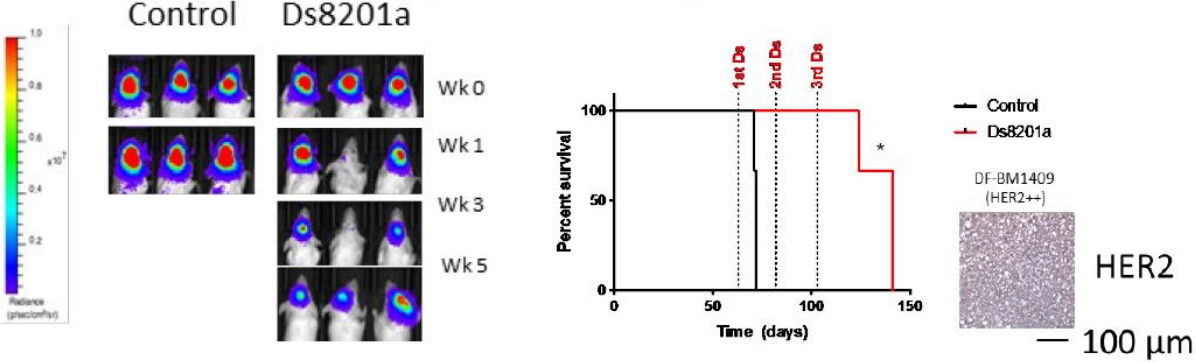
**Consistent with improvement in time to New brain lesion in Her2Climb.....**



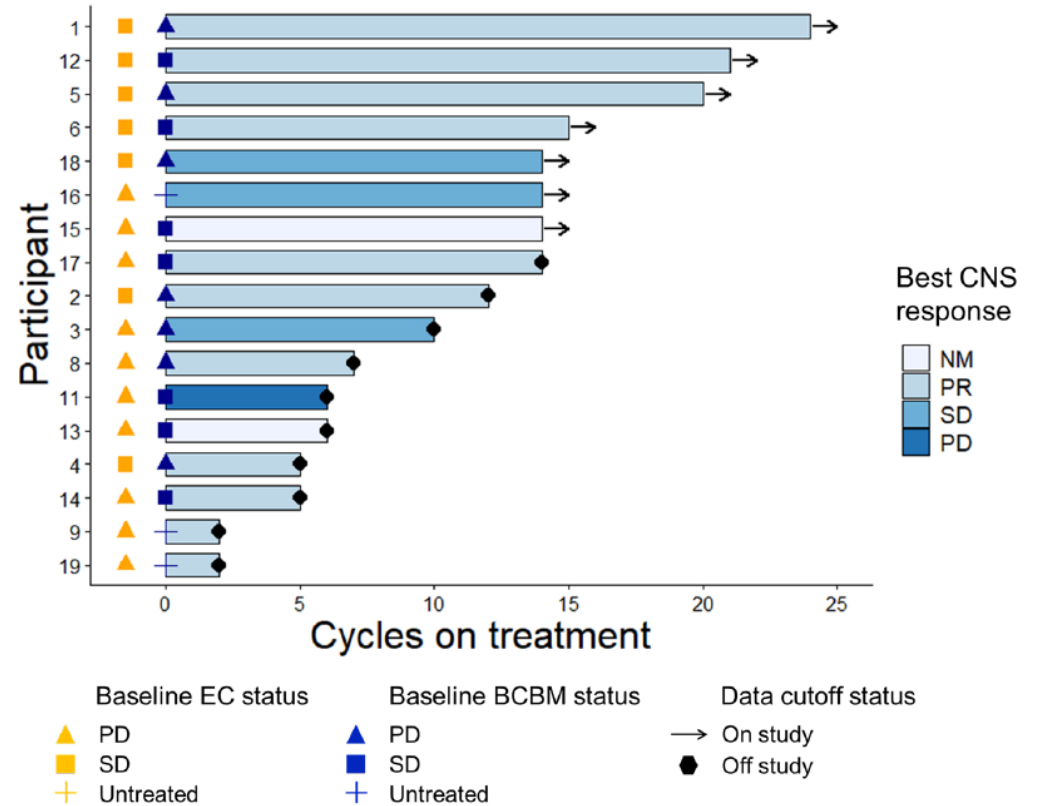
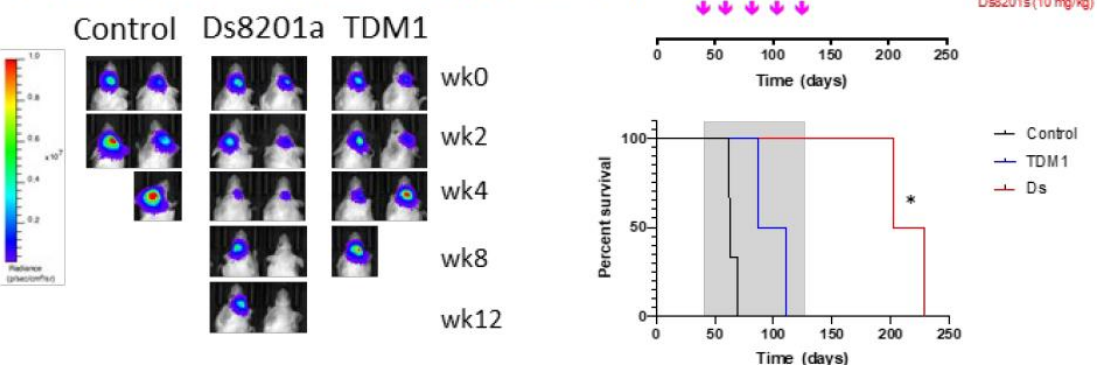


# TDxd in Her2+ Active Breast Cancer Brain Metastases

DF-BM 1409 ER+ HER2-low (IHC 2+, FISH negative)



DF-BM355TDM1-resistant model (HER2 3+)



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)

Study	Retro/Pro	n	CNS Status(es)	CNS-ORR	OS/PFS
<i>Kabraji et al. CCR 2023</i>	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 ( <i>Bartsch et al. Nat Med 2022</i> )	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 ( <i>Hurvitz et al. ESMO 2023</i> )	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 ( <i>Lin N et al. ESMO, 2024</i> )	Prospective	n=263	Stable or Active (Untreated or Progressive) HER2+ BrM	71.7% (All) (79.2% Stable; 62.3% Active)	

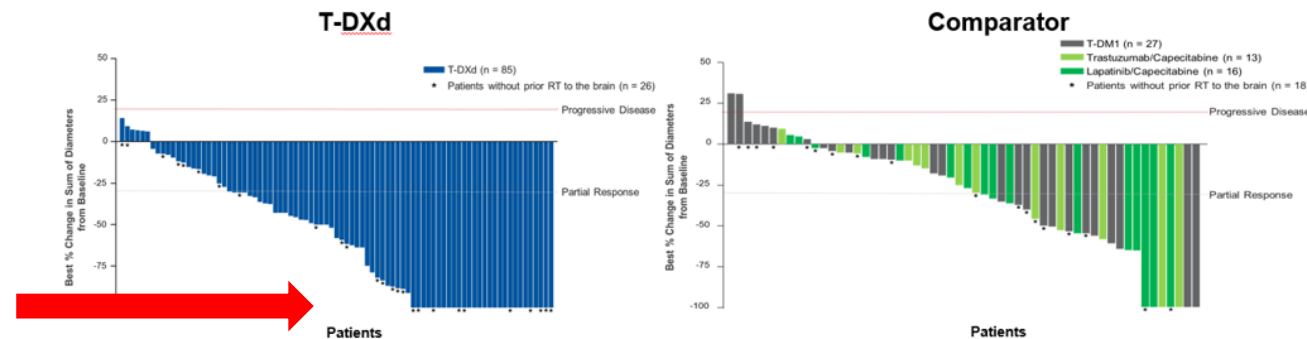


DESTINY-Breast01, -02, and -03

Hurvitz et al. ESMO 2023.

T-DXd Clinical Performance in HER2+ Breast Cancer Brain Metastases  
iORR ~70% across studies  
Including CR's

### 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



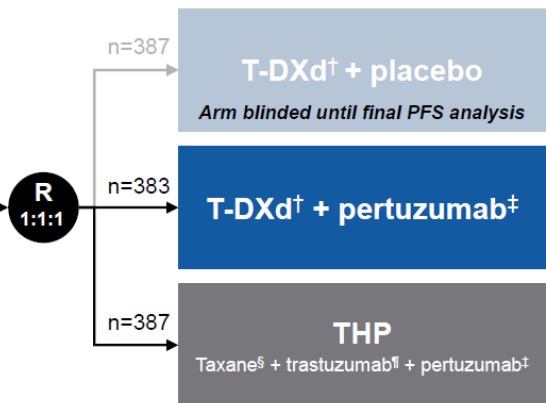
# Trastuzumab Deruxtecan in *First Line* Her2+ MBC

## DESTINY-Breast09 study design

A randomized, multicenter, open-label,\* Phase 3 study (NCT04784715)<sup>1,2</sup>

### 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



### Endpoints

#### Primary

- PFS (BICR)

#### Key secondary

- OS

#### Secondary

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

### Stratification factors

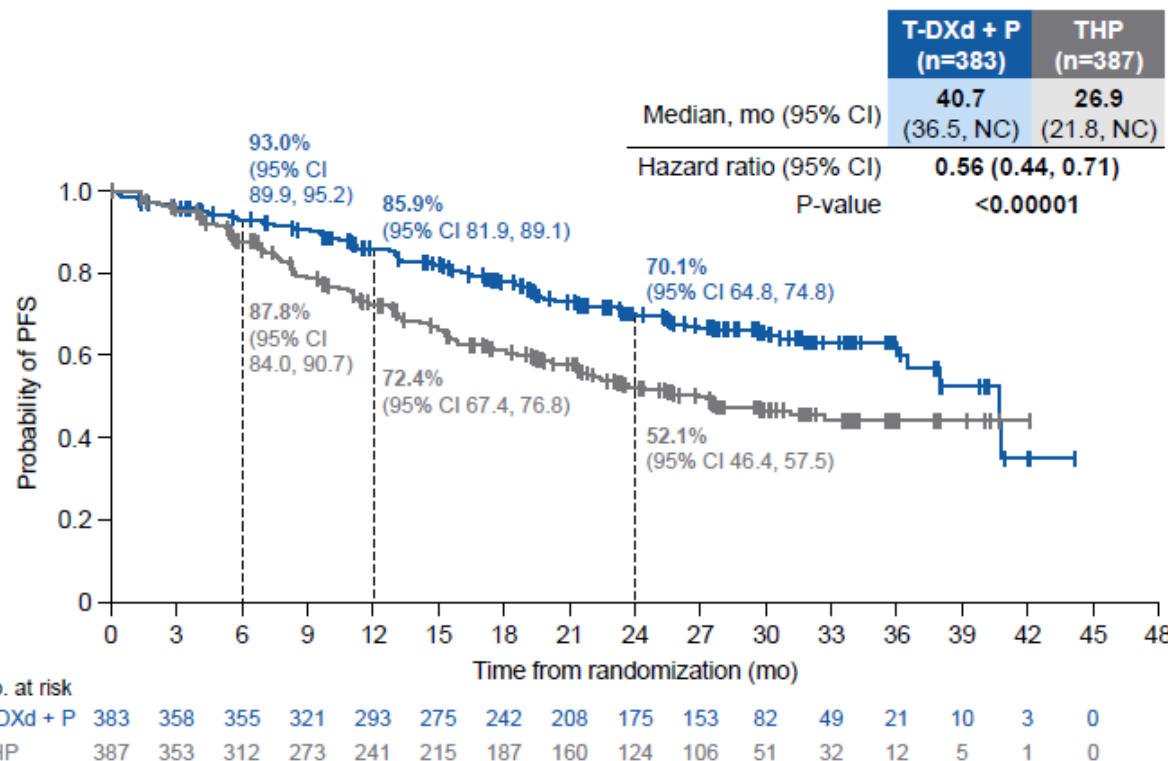
- De-novo (~52%) vs recurrent a/mBC
- HR+ (~54%) or HR-
- PIK3CAm detected (~31%) vs not detected

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

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?**

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

## DESTINY-Breast09 interim analysis (DCO February 26, 2025) PFS by BICR: primary endpoint<sup>1</sup>





# Prevention of CNS Metastases in ER+/Her2+MBC

## PATINA: Randomized, Open-Label, Phase III Trial (AFT-38)<sup>1,2\*</sup>



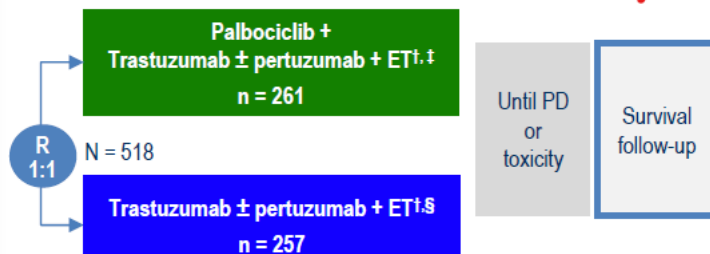
**Objective:** To evaluate the addition of palbociclib to anti-HER2 and ET for patients with HR+/HER2+ breast cancer

### 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

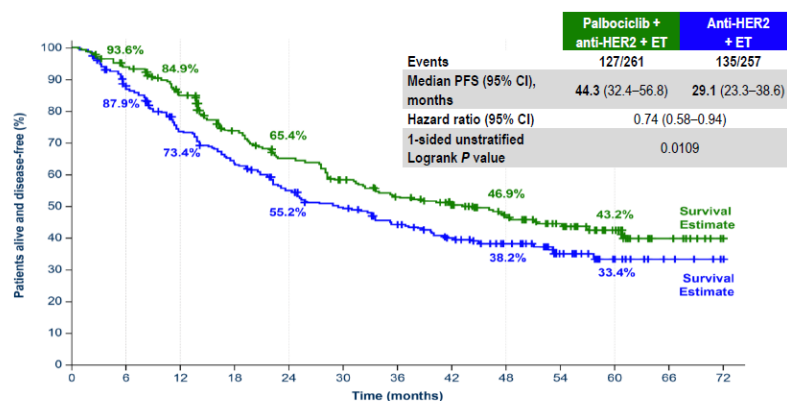
- OS
- 3- and 5-year survival probabilities
- ORR / DOR / CBR
- Safety
- PRO
- **Incidence of CNS metastases**

Lower incidence of CNS Metastases At 36 months:

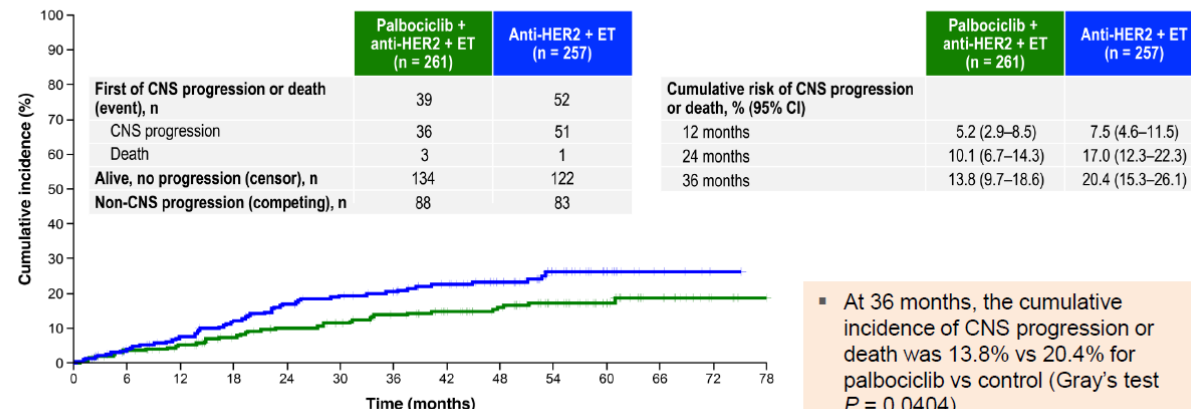
- 13.8% for Palbo + ET + HP
- 20.4% for ET + HP

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

## PATINA Primary Endpoint: Investigator-Assessed PFS<sup>1</sup>



## Cumulative Incidence of CNS Progression<sup>a</sup> or Death All Randomized Patients

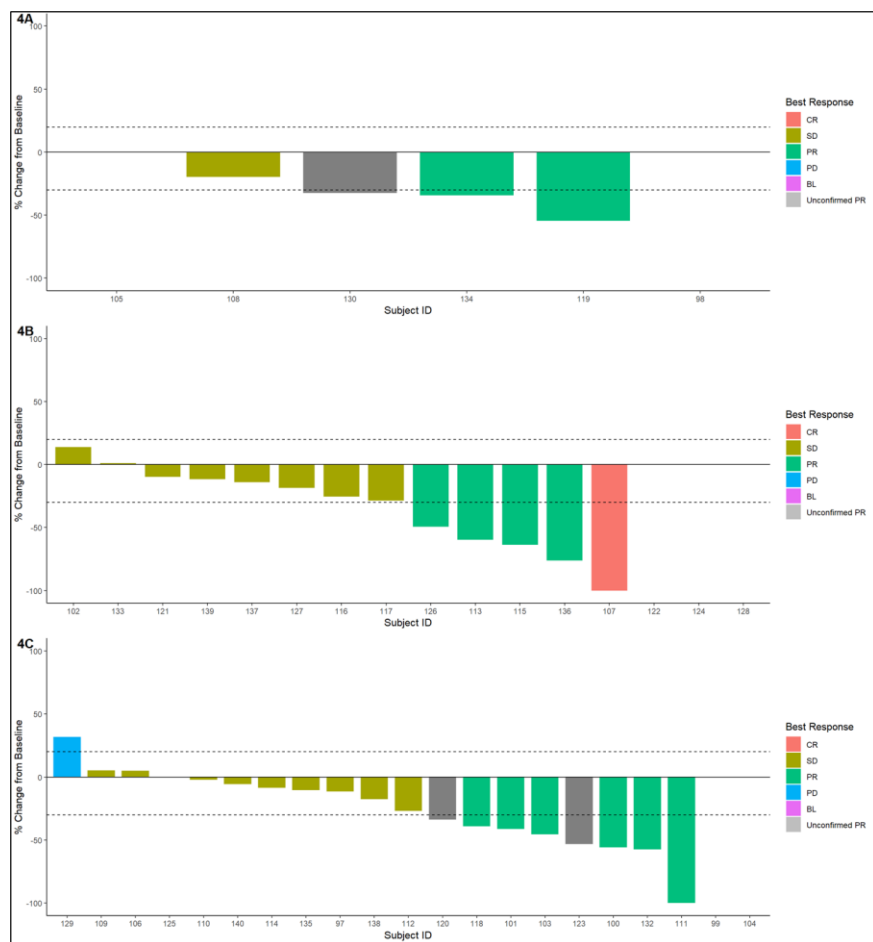


At 36 months, the cumulative incidence of CNS progression or death was 13.8% vs 20.4% for palbociclib vs control (Gray's test P = 0.0404).



# 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)
<b>CNS ORR</b>	<b>33.3% (4.3-77.7%)</b>	<b>29.4% (10.3-56.0%)</b>	<b>28.6% (11.3-52.2%)</b>
<b>CNS CR + PR + SD ≥6 mos</b>	<b>50% (11.8-88.2%)</b>	<b>35.3% (14.2-61.7%)</b>	<b>33.3 (14.6-57.0%)</b>

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



# PATRICIA: High dose trastuzumab with pertuzumab for Her2+ BCBM

Pertuzumab plus high-dose trastuzumab for HER2-positive breast cancer with brain metastases: PATRICIA final <sup>N = 39 pts</sup> efficacy data

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

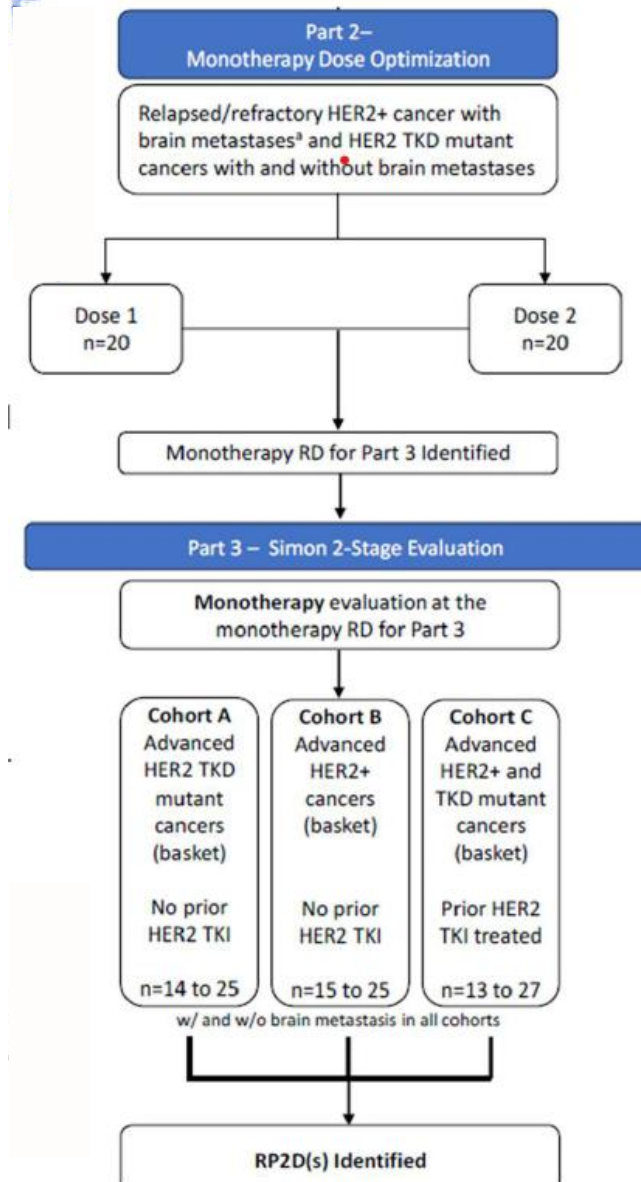
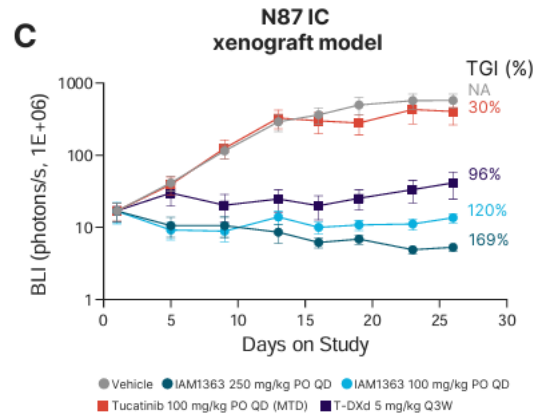
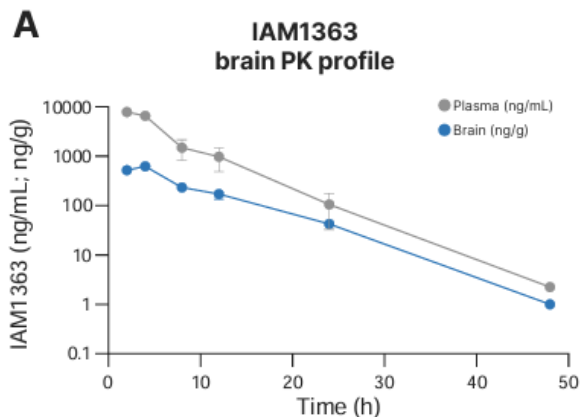
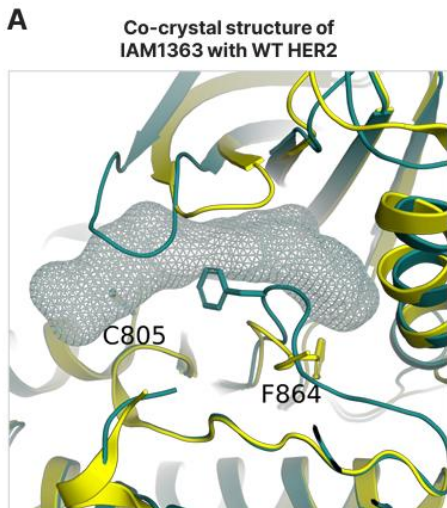
- Another option is high dose Trastuzumab (6mg/kg IV q 1 week) plus standard 3 week dosing of Pertuzumab per the PATRICIA Study
  - **Intracranial ORR = 11%; CNS PFS = 4.6 months; OS = 27.2 months**
  - No clinically meaningful changes in LVEF; only 1 pt discontinued therapy due to Grade 3 decline in 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 <sup>1</sup>	
			Cell pHER2 vs. pEGFR <sup>7</sup>	Biochemical HER2 vs. EGFR <sup>8</sup>
Tucatinib (Pfizer)	Marginal <sup>2</sup>	No <sup>3</sup>	>1200	-
Zongertinib (BI)	No <sup>4</sup>	Yes	-	20
ZN-1041 (Zion/Roche) <sup>5</sup>	Yes	No <sup>6</sup>	-	-
ELVN-002 <sup>5</sup>	Moderate	Yes	180 <sup>9</sup>	47 <sup>9</sup>
NVL-330 <sup>5</sup>	Yes	Yes	96 <sup>9,10</sup>	-
IAM1363	Yes	Yes	2800	5200





# The challenge of Her2+ Leptomeningeal Disease



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## NCCN Guidelines Version 3.2025 Leptomeningeal Metastases

### LEPTOMENINGEAL METASTASES: SYSTEMIC THERAPY

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

## ARTICLES

<https://doi.org/10.1038/s41591-022-01935-8>

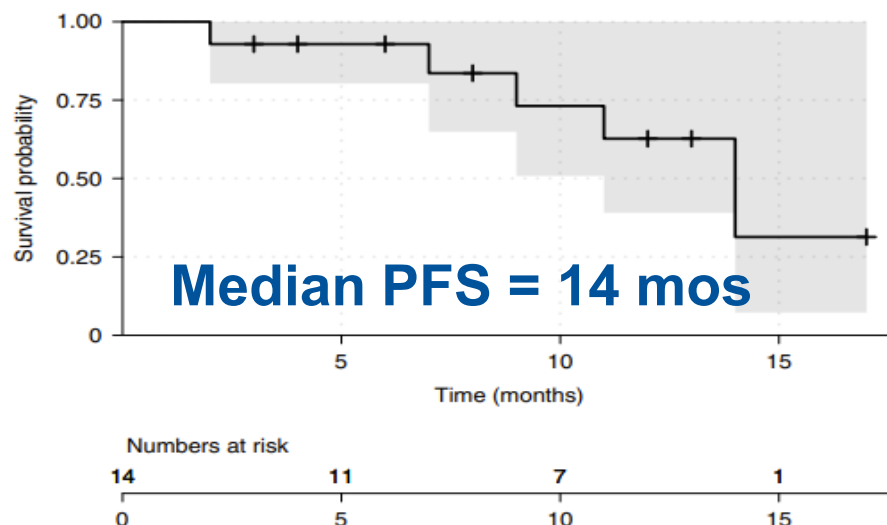
nature  
medicine

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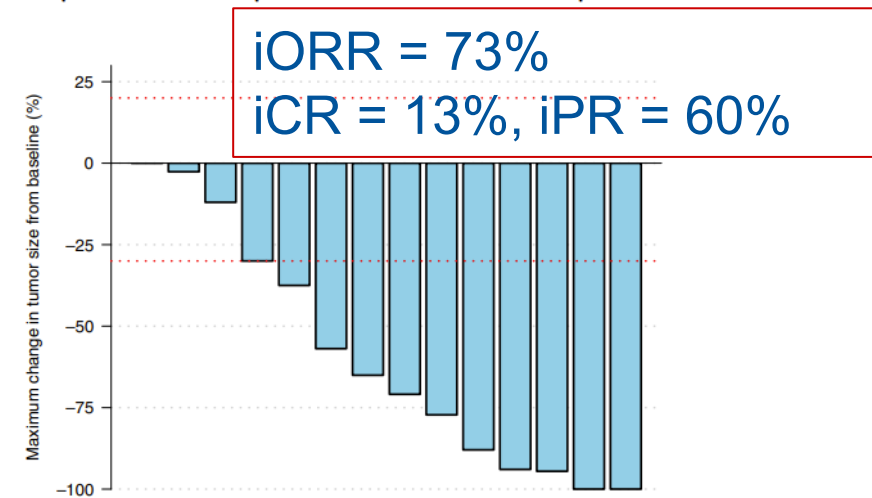
### OPEN

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

Rupert Bartsch<sup>1</sup>, Anna Sophie Berghoff<sup>b,1</sup>, Julia Furtner<sup>2</sup>, Maximilian Marhold<sup>b,1</sup>,



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



**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

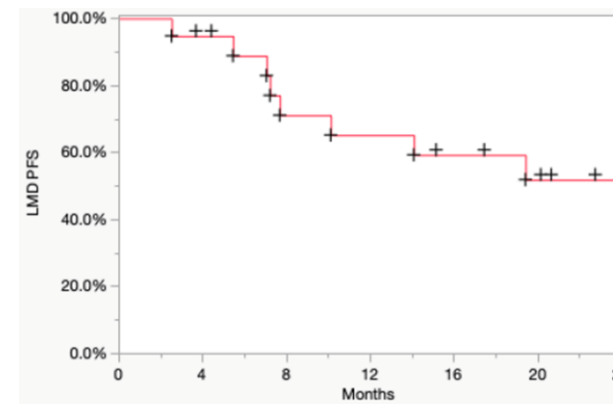
## Historical Controls IT trastuzumab

### 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
Oberkampff et al 2023	Phase II Trastuzumab IT 150mg once a week	N= 19	LM-PFS = 5.9 mo OS = 7.9 mo

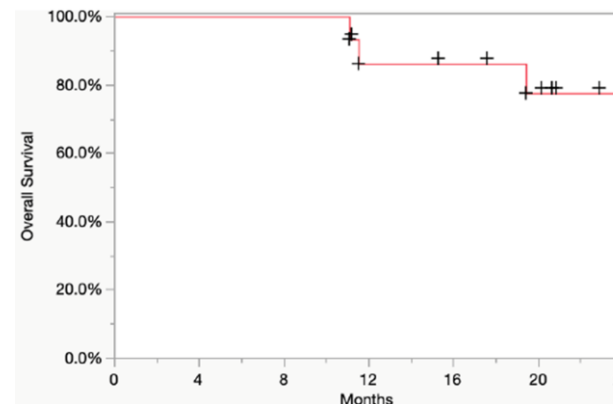
Slide courtesy of Sarah Sammons, MD

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



12m LM-PFS  
65%  
Median MR

No at Risk: 20 18 13 12 10 8 5



12m OS  
86%  
Median MR

No at Risk: 20 18 17 13 12 10 6

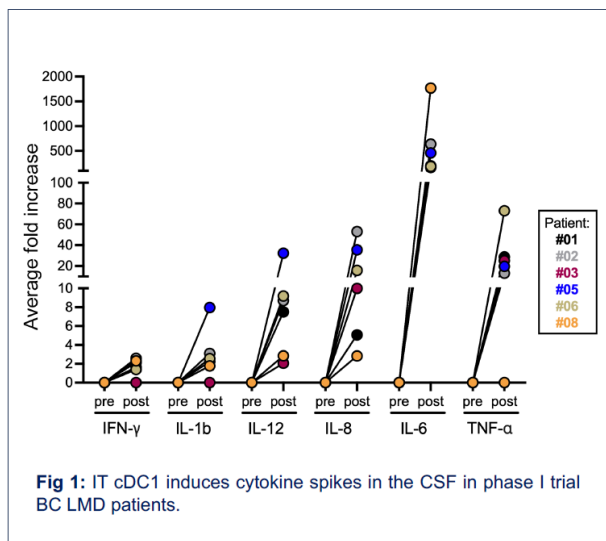
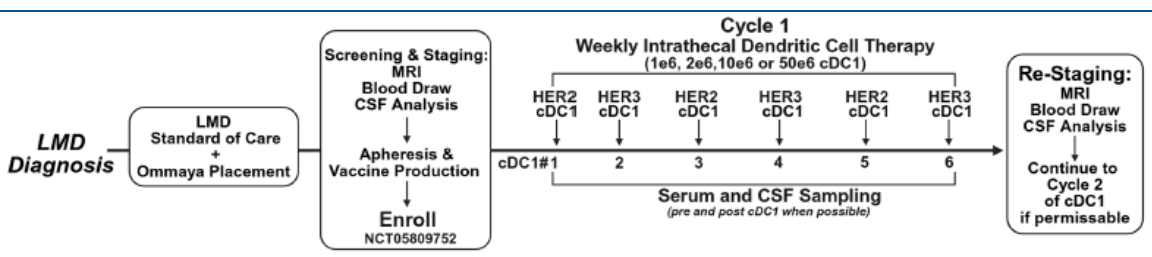
What concurrent Therapies?  
Prior Therapies?

Ahmed K et al SABCS 2025.



# Novel Intrathecal LMD Strategies to Watch

## IT Dendritic Cell Therapy



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 <sup>+</sup> /ERBB2 <sup>+</sup>	Whole brain	NA	PR
2	50s	90	Radiographic findings	Trastuzumab plus pertuzumab	20	HR <sup>-</sup> /ERBB2 <sup>+</sup>	Prior whole brain and SRS	Grade 1 headache	Stable disease
3	50s	80	CSF and radiographic findings	Sacituzumab govitecan	40	HR <sup>-</sup> /ERBB2 <sup>+</sup>	Whole brain	Grade 2 fatigue	Stable disease
4	40s	60	CSF and radiographic findings	Trastuzumab plus pertuzumab	80	HR <sup>-</sup> /ERBB2 <sup>+</sup>	Whole brain	Grade 1 arthralgia and extremity pain	CR
5	50s	90	Radiographic findings	Trastuzumab deruxtecan	80	HR <sup>-</sup> /ERBB2 <sup>+</sup>	Prior whole brain	Grade 1 fatigue and headache	PR
6	40s	90	Radiographic findings	Trastuzumab	80	HR <sup>-</sup> /ERBB2 <sup>+</sup>	Prior whole brain and FSRS	Grade 1 fatigue and nausea	Stable disease
7	60s	80	Radiographic findings	Trastuzumab deruxtecan	80	HR <sup>-</sup> /ERBB2 <sup>+</sup>	FSRS	Grade 1 paresthesia	CR
8	30s	90	Radiographic findings	Trastuzumab	80	HR <sup>+</sup> /ERBB2 <sup>+</sup>	Whole brain	NA	PR
9	50s	90	Radiographic findings	Trastuzumab plus pertuzumab	80	HR <sup>-</sup> /ERBB2 <sup>+</sup>	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!

