Management of HER2-Positive BC with CNS Metastases

Erika Hamilton, M.D.

Director Breast Cancer Research

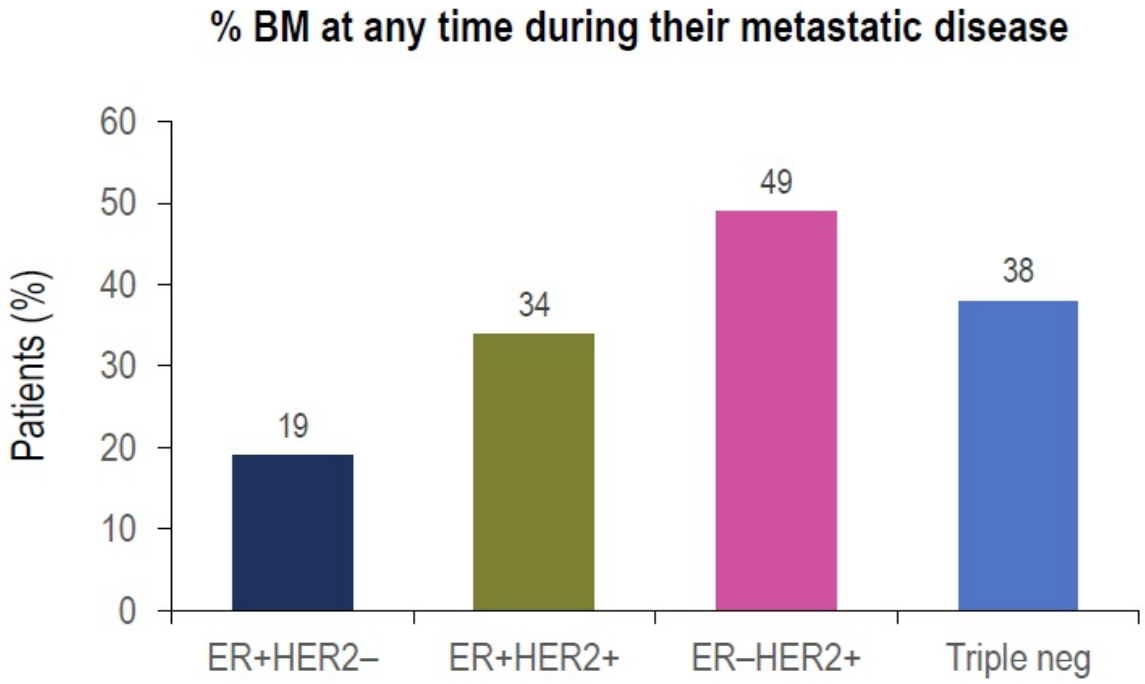
Sarah Cannon Research Institute/Tennessee Oncology

Nashville, TN

SARAH CANNON

Breast cancer and Brain Metastases

- Breast cancer has 2nd highest incidence of brain metastasis among all cancers
- Risk and incidence of brain mets varies depending on BC subtype



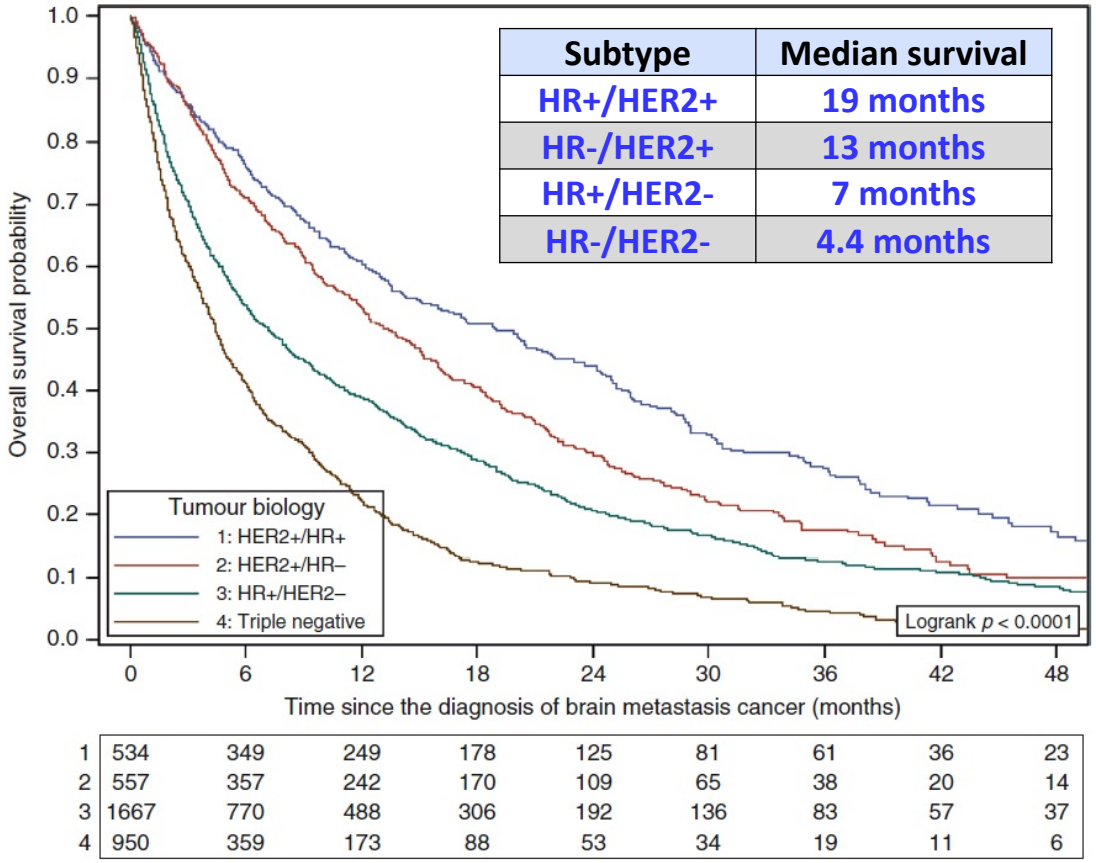
- The brain is frequently the 1st site of relapse in HER2+ BC patients treated with trastuzumab, whether administered in the adjuvant or metastatic setting

SARAH CANNON

Darlix A, *et al*. Br J Cancer 2019;121:991-1000;
Pasquier D, *et al.* Eur J Cancer 2020;125:22e30.

Survival in BC brain mets patients based on subtype

ESME MBC database
CNS mets cohort (n=4118)



Subtype	Median survival
HR+/HER2+	19 months
HR-/HER2+	13 months
HR+/HER2-	7 months
HR-/HER2-	4.4 months

NCI SEER registry
BCBM cohort (n=1268)

5-year percent survival analysis

	BCBM	All BC
HR+/HER2-	9.8 (6.9-13.3)	86.3 (86.2-86.5)
HR+/HER2+	21.9 (16.0-28.4)	85.6 (85.1-86.0)
HR-/HER2+	14.3 (8.5-21.5)	79.7 (79.0-80.4)
HR-/HER2-	**3.6 (1.6-6.9)**	**71.9 (71.4-72.4)**
All subtypes	11.3 (9.2-13.6)	84.3 (84.1-84.4)

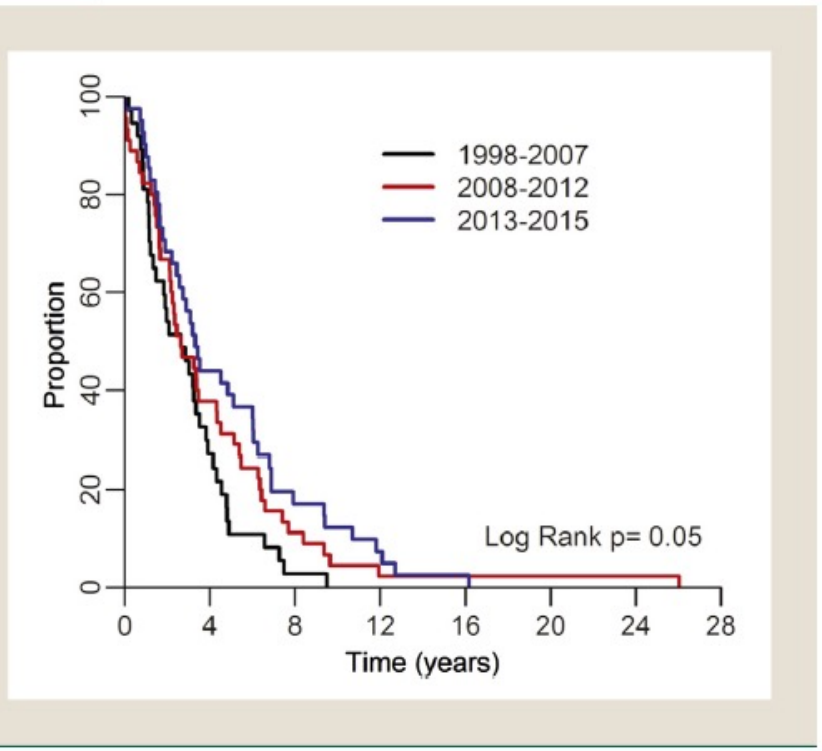
BCBM= breast cancer brain mets

@ErikaHamilton9

SARAH CANNON

Darlix A, *et al*. Br J Cancer 2019;121:991-1000.
Devanaboyina M. et al. ASCO 2021 Abstract #1031

Brain mets and anti-HER2 therapy



- Time from initial diagnosis of BC→ brain mets: ↑ ~ 9 months from 1998-2007 cohort to 2013-2015 cohort
  - ↑ time from initial diagnosis to metastatic disease
  - ↑ time from 1st metastatic diagnosis to brain mets diagnosis

SARAH CANNON

Mounsey LA et al. Clinical Breast Cancer 2017; 18:29-37

CNS penetrance of approved agents for HER2+ MBC

Although CSF levels of **neratinib and trastuzumab** are low, there is evidence that it accumulates in the brain tissue

Ratio of trastuzumab levels in serum: CSF 420:1 pre- ***vs.*** 76:1 post-radiation[1]

Accumulation of trastuzumab was 17.5-fold higher in brain metastases than in normal brain tissue[2]

Neratinib levels were very low in CSF(<1.5ng/mL), although it was detected in plasma (34.3ng/mL)[3]

However neratinib has been shown to accumulate in the actual brain tissue, ~10X levels seen in plasma[3]

Tucatinib on the other hand does appear to have greater concentration in CSF

Tucatinib easily found in CSF 0.57- 25ng/mL (IC_{50} of tucatinib against HER2= 3.3ng/mL)[4]

Similar CSF: plasma ratios that are consistent over time[4]

@ErikaHamilton9

1. Stemmler HJ et . 2007
2. Dijkers EC et al. 2010
3. Freedman RA et al. 2020
4. Stringer-Reasor EM et al. ASCO 2021

SARAH CANNON

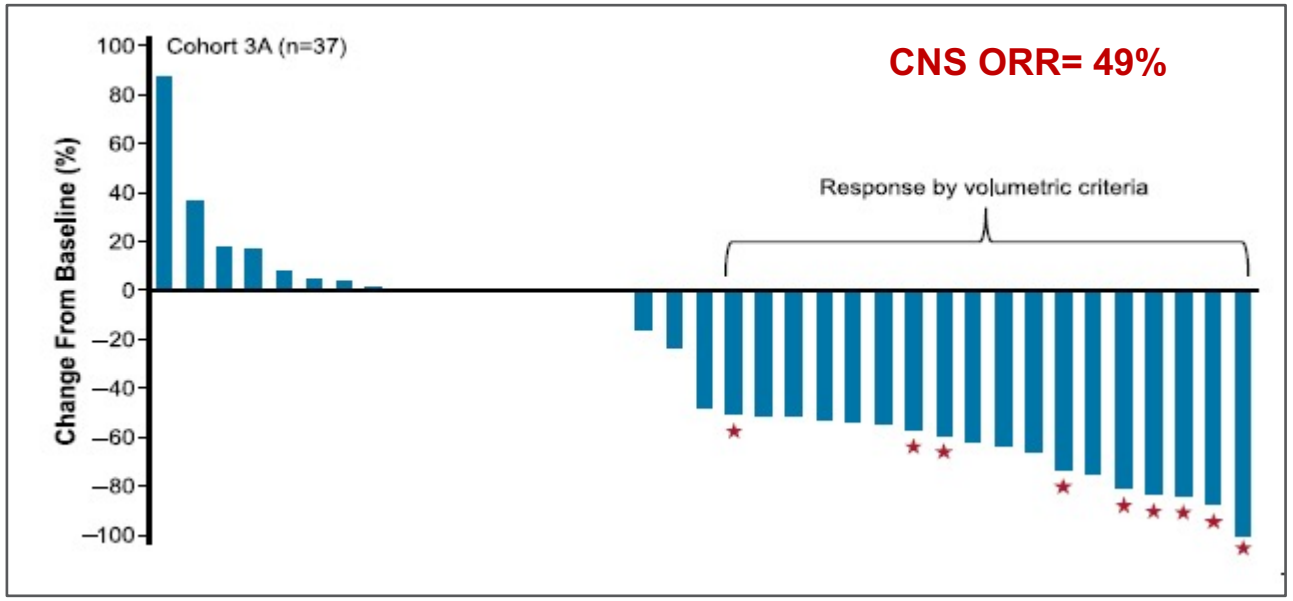
HER2- TKIs

SARAH CANNON

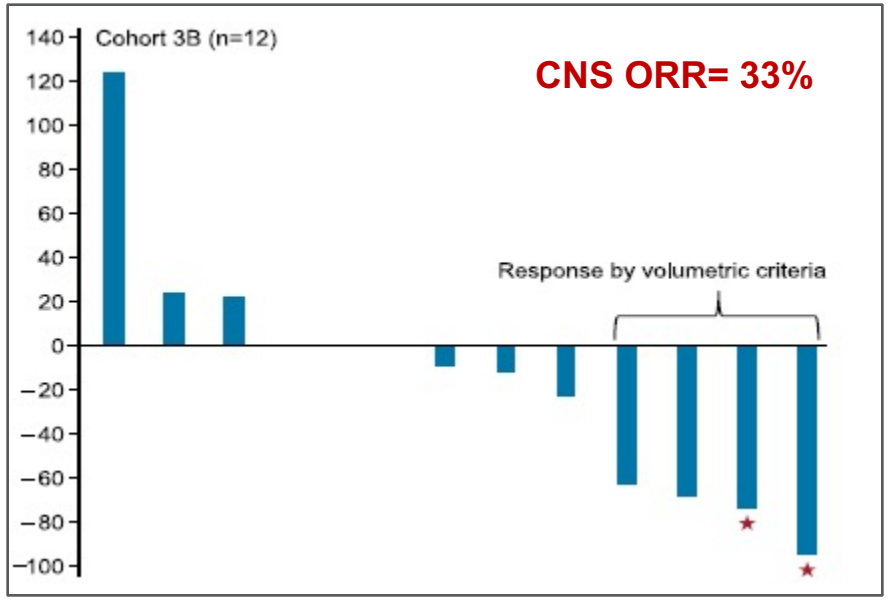
Neratinib+capecitabine for HER2+ BC pts with brain mets

TBCRC 022: Phase II study of Neratinib+capecitabine in HER2+ MBC pts with brain mets

No prior treatment with Lapatinib



Prior treatment with Lapatinib



★ Patients who also had a CNS response by RANO-brain mets criteria

@ErikaHamilton9

SARAH CANNON

Freedman RA *et al*. JCO. 2019;37:1081

NALA: Outcomes in patients with CNS disease

NALA: Phase III study of Neratinib+capecitabine vs Lapatinib+capecitabine in HER2+ MBC

Table 1. Efficacy outcomes in patients with CNS disease at baseline

	CNS metastases at baseline (n=101)		
	N+C (n=51)		L+C (n=50)
Progression-free survival[a]			
Hazard ratio (95% CI)		0.66 (0.41–1.05)	
P-value		0.0741	
Restricted mean PFS[b], months	7.8		5.5
Difference, months		2.3	
Overall survival			
Hazard ratio (95% CI)		0.90 (0.59–1.38)	
P-value		0.6352	
Restricted mean OS[b], months	16.4		15.4
Difference, months		1.0	

CNS-specific outcomes	N+C (n=51)		L+C (n=50)
CNS progression-free survival			
Median, months	12.4		8.3
Hazard ratio (95% CI)		0.62 (0.32–1.18)	
P-value		0.143	

81 patients (80.2%) had received prior CNS-directed radiotherapy and/ or surgery

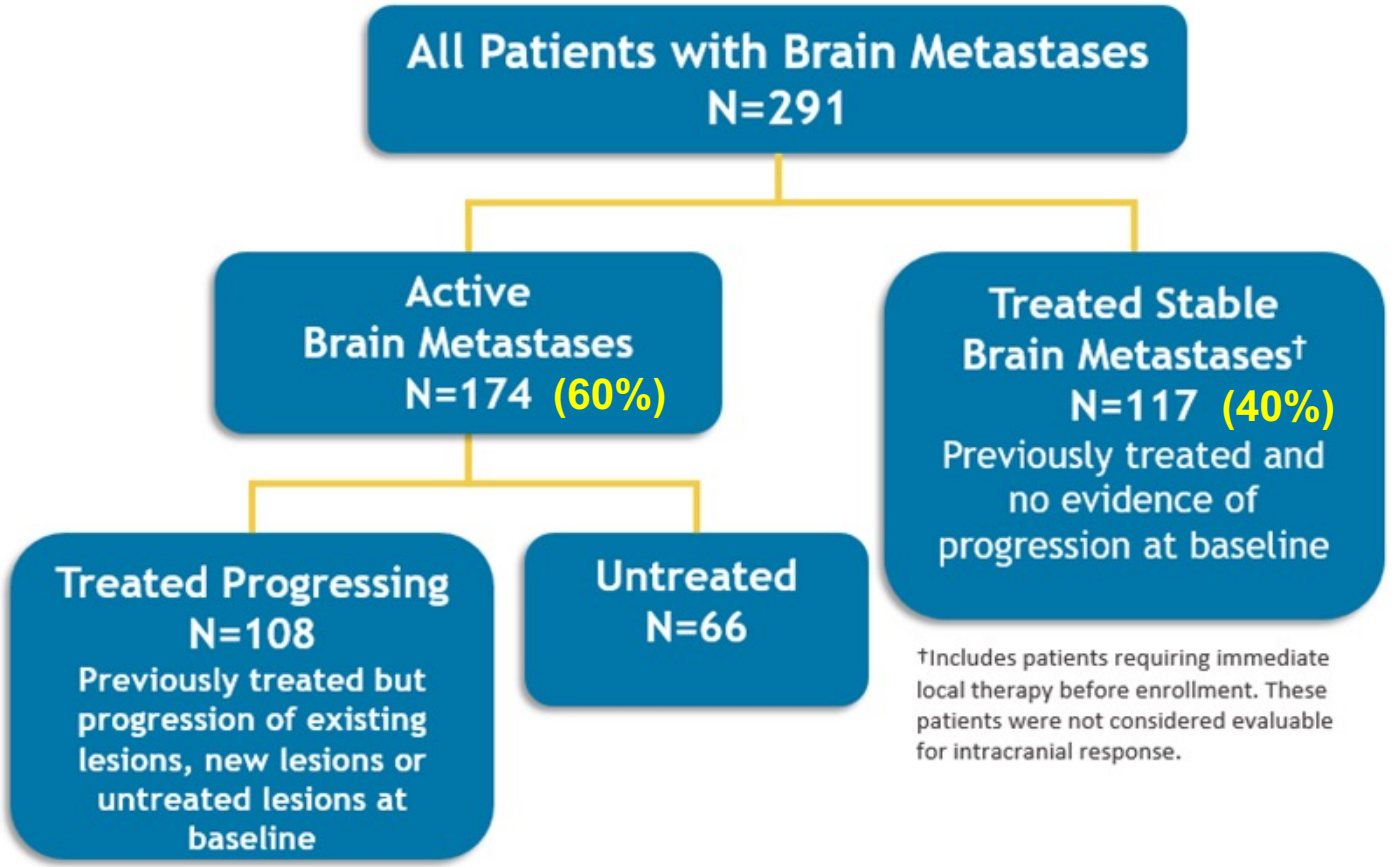
SARAH CANNON

Saura C et al. SABCS 2020 Abstract PD13-09; Hurvitz *Oncologist*. 2021;26(8):e1327-e1338.

HER2CLIMB: CNS mets subset

48% of the patients enrolled on the trial had brain mets

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*



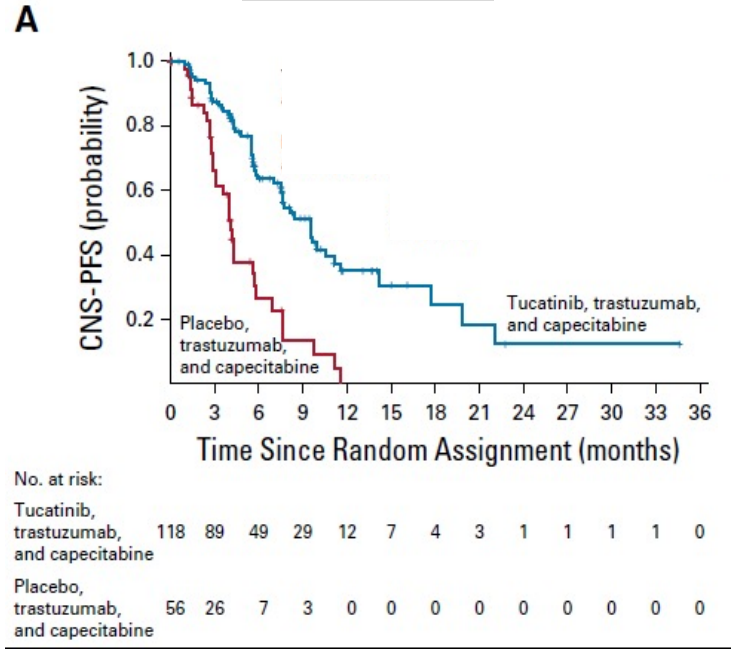
*These patients were included in the Treated Stable group for analysis.

SARAH CANNON

Lin NU et al ASCO 2020

HER2CLIMB: CNS - PFS & OS benefit in patients with brain mets

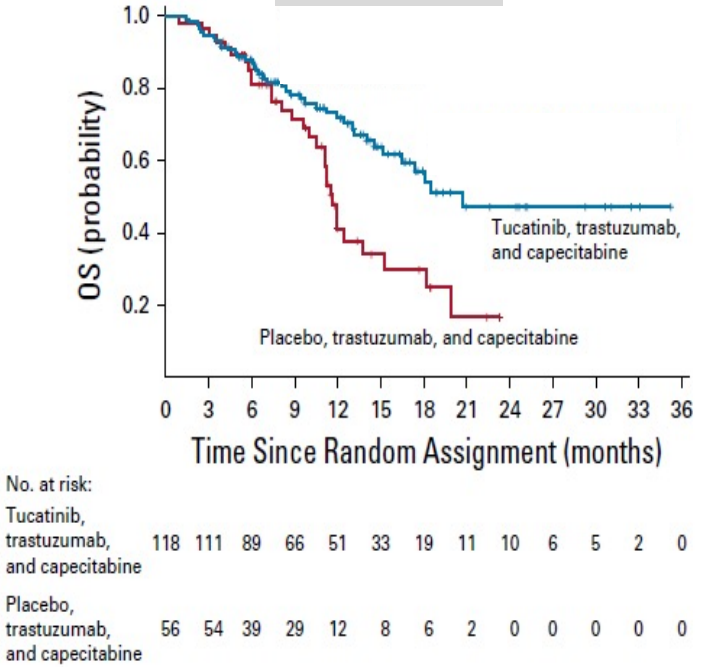
CNS-PFS



	Median PFS (months)
Tucatinib arm	9.5
Placebo arm	4.1
	HR 0.36 p <0.00001

Risk of progression or death in patients with active brain mets was reduced by 64%

CNS-OS



	Median OS (months)
Tucatinib arm	20.7
Placebo arm	11.6
	HR 0.49 p 0.004

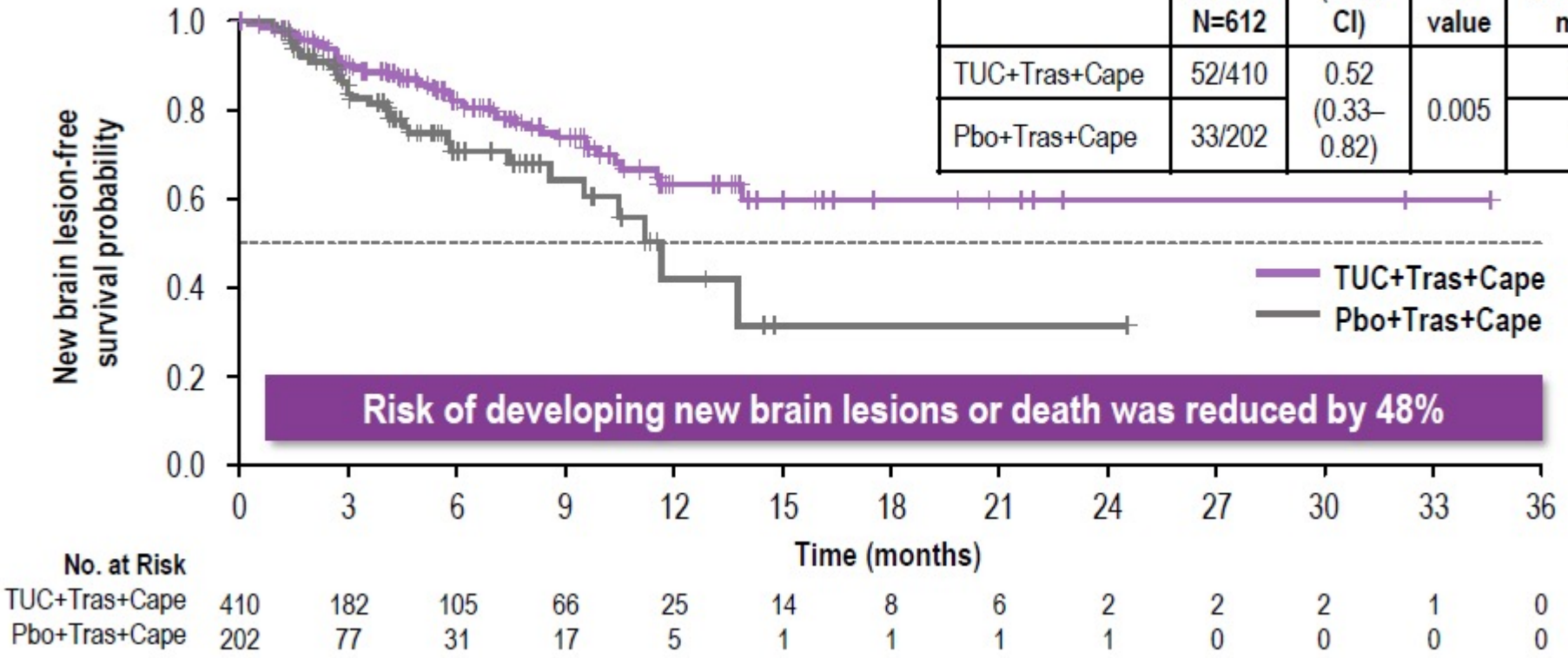
Risk of death in patients with active brain mets was reduced by 51%

SARAH CANNON

Lin NU et al. JCO 2020

HER2CLIMB: Time to new brain lesions or death (all patients)

	Events N=612	HR (95% CI)	P value	Median new brain lesion-free survival, months (95% CI)
TUC+Tras+Cape	52/410	0.52 (0.33–0.82)	0.005	NR (13.9–NR)
Pbo+Tras+Cape	33/202			11.7 (9.5–NR)



@ErikaHamilton9

SARAH CANNON

Bachelot T et al ESMO 2020

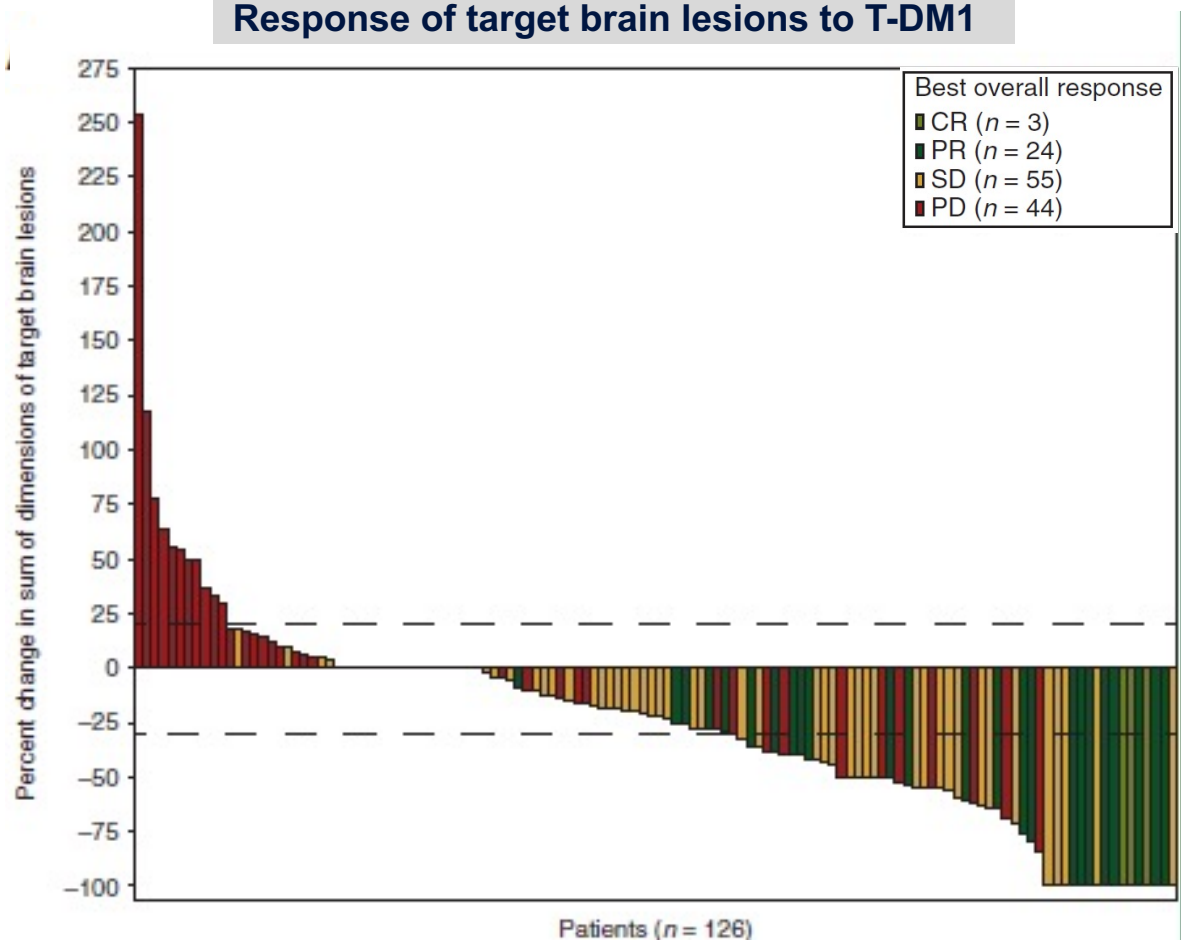
HER2-ADCs

SARAH CANNON

KAMILLA: T-DM1 in HER2+ brain mets subset

Phase IIIb single arm study of T-DM1 in HER2+ MBC pts treated with prior anti-HER2 therapy and chemotherapy (N=2002)

Response of target brain lesions to T-DM1



Exploratory analysis of T-DM1 in subset of patients with measurable brain lesions (n=126)

- ORR: 21.4%
- CBR: 42.9%

- Median PFS*: 5.5 months
- Median OS*: 18.9 months

*n= 398 pts with baseline brain mets

SARAH CANNON

Montemurro F *et al*. Annals of Onc. 2020;31:1350

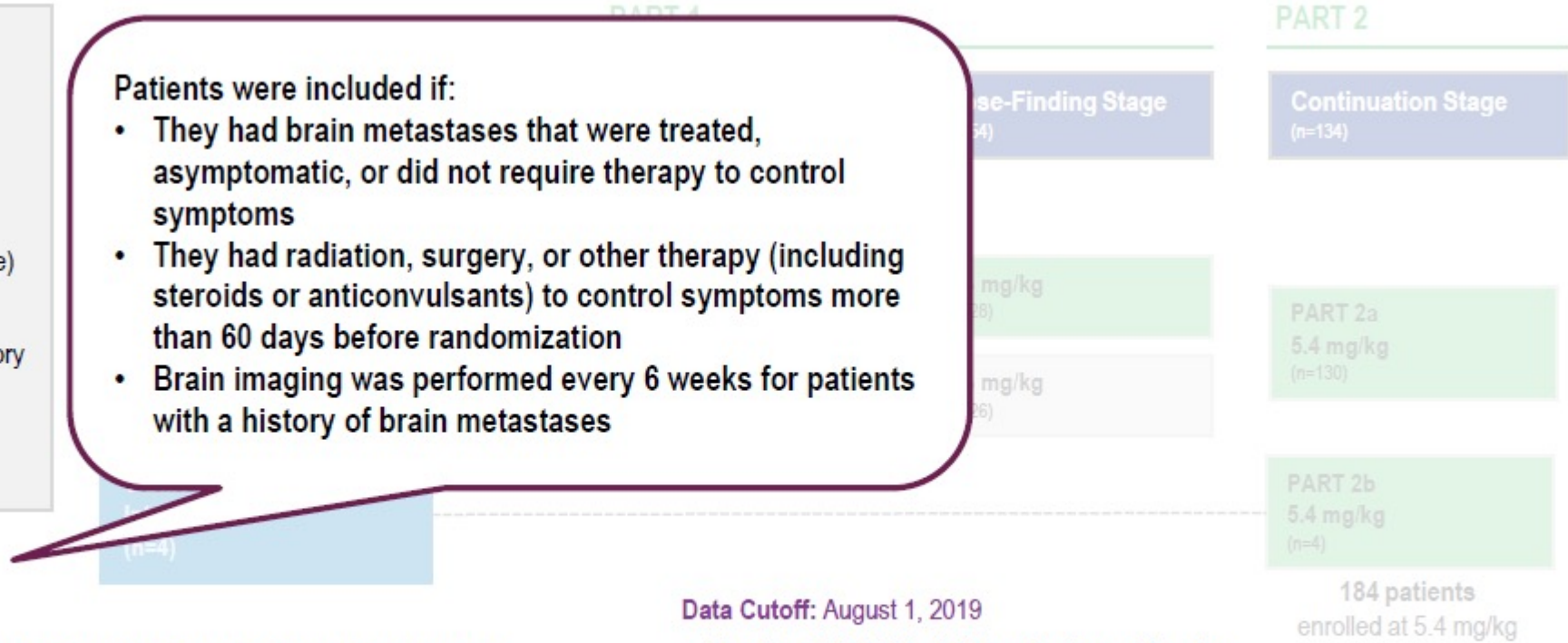
DESTINY Breast-01: CNS Subgroup

Population

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2 positive (centrally confirmed on archival tissue)
- **Prior T-DM1**
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

Patients were included if:

- **They had brain metastases that were treated, asymptomatic, or did not require therapy to control symptoms**
- **They had radiation, surgery, or other therapy (including steroids or anticonvulsants) to control symptoms more than 60 days before randomization**
- **Brain imaging was performed every 6 weeks for patients with a history of brain metastases**



Endpoints

- **Primary:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK and safety

Data Cutoff: August 1, 2019

- **24 patients (13.0%) had CNS metastases at baseline**
  - 11 (45.8%) ongoing
  - 13 (54.2%) discontinued, primarily for progressive disease (6/24, 25.0%)

SARAH CANNON

Jerusalem G et al ESMO Breast 2020

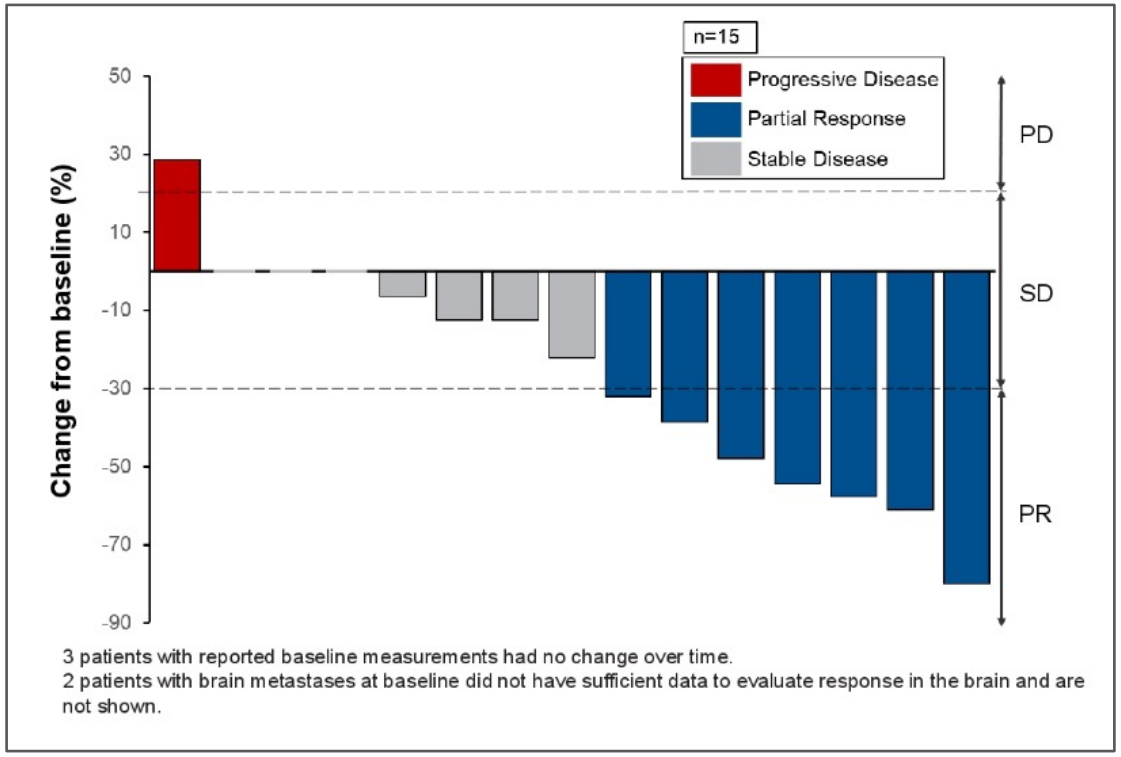
DESTINY Breast-01: Efficacy of T-DXd

Intent-to-treat analysis	CNS subgroup† (n=24)	All patients (N=184)
Confirmed ORR by ICR, % (n) [95% CI]	**58.3 (14)** [36.6–77.9]	**60.9 (112)** [53.4–68.0]
CR	4.2 (1)	6.0 (11)
PR	54.2 (13)	54.9 (101)
SD	33.3 (8)	36.4 (67)
PD	4.2 (1)	1.6 (3)
Not evaluable	4.2 (1)	1.1 (2)
DCR, % (95% CI)	91.7 (22)	97.3 (93.8–99.1)
Median duration of response, months (95% CI)	16.9 (5.7–16.9)	14.8 (13.8–16.9)
Median time to response, months (95% CI)	2.8 (1.3–4.1)	1.6 (1.4–2.6)
Median PFS, months (95% CI)	18.1 (6.7–18.1)	16.4 (12.7–NE)

Jerusalem G et al ESMO Breast 2020

DESTINY Breast-01: Efficacy with T-DXd

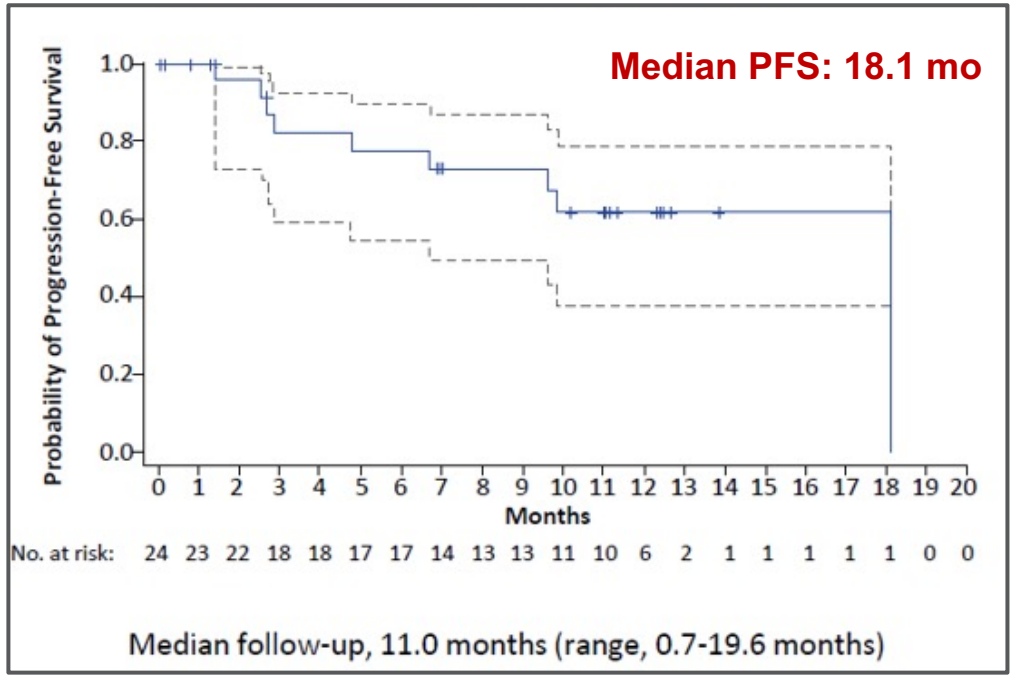
Best response in brain lesions in CNS subgroup[1]



CNS subgroup N=24
Brain lesions at BL n=17
Evaluable for response in brain n=15

❖ 7/17 pts with brain lesions at BL had a PR in CNS lesions (41.2%)

PFS in CNS subgroup[2] (n=24)



- Confirmed ORR in CNS subgroup: 58.3%
- Median DoR in CNS subgroup: 16.9 months

@ErikaHamilton9

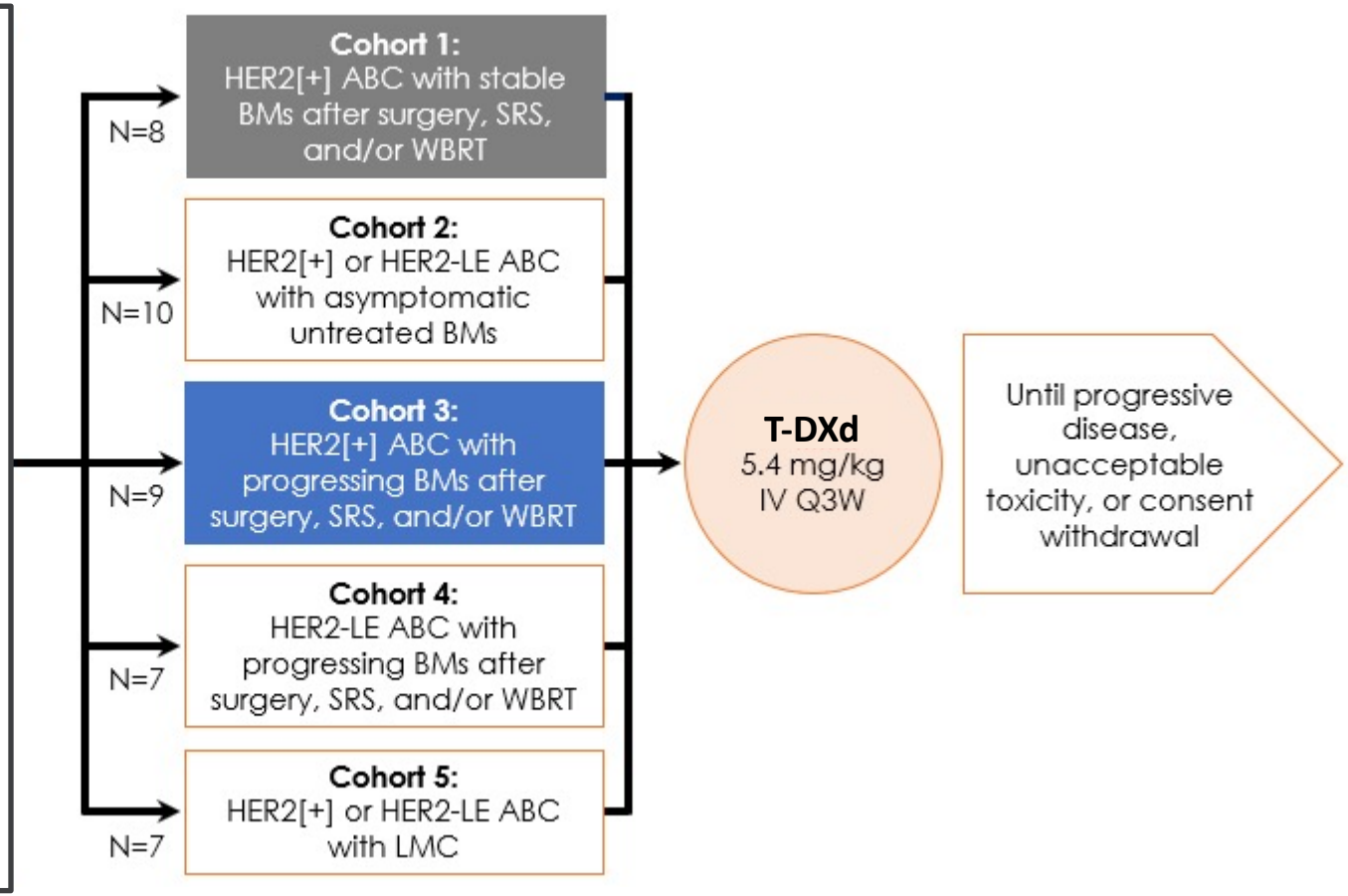
SARAH CANNON

1. Jerusalem G et al ASCO 2021; Abstract 526
2. Jerusalem G et al ESMO Breast 2020

DEBBRAH: Ph 2 trial of T-DXd in pts with HER2+/ HER2-low MBC & history of brain mets

Cohorts 1 and 3 enrolled patients with **HER2+ MBC** and stable or progressing brain mets respectively

- HER2+ /HER2-low MBC with stable or active brain mets and/or leptomeningeal disease
- Pts with HER2+ MBC
  - Prior tx with a taxane and ≥1 prior line for MBC
- Pts with HER2-low MBC
  - ≥1 prior line of chemo for MBC
- Cohorts 2, 3, 4: Measurable brain lesions
- Cohort 5: LMC with CSF+ cytology



@ErikaHamilton9

SARAH CANNON

Vaz Batista M et al. SABCS 2021

DEBBRAH: Outcomes & Safety

Efficacy in Cohort 1 (stable brain mets)

1. **7/8 pts (87.5%) alive without PD at 16 weeks**
   Trial met primary EP

2. **At data cut-off 5/8 pts had not experienced progression or death**

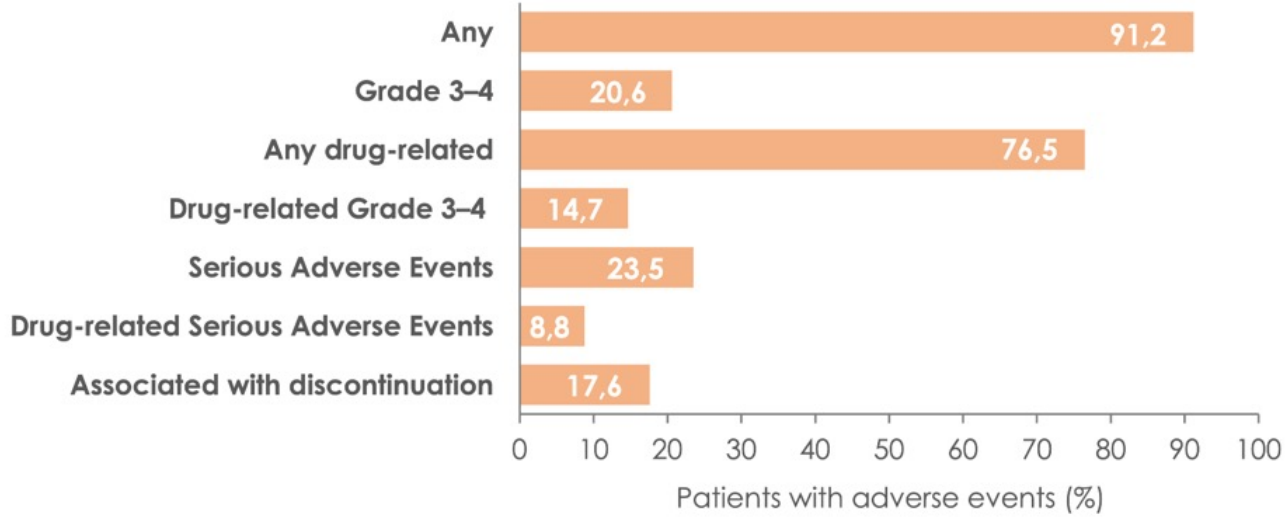
Efficacy in Cohort 3 (progressing brain mets)

1. **ORR-IC reported in 4/9 pts (44.4%)**
   Trial met primary EP

2. **CBR-IC: 55.6%**

3. **At data cut-off 4/9 pts had not experienced progression or death**

Safety (Cohorts 1-5)



T-DXd demonstrated preliminary efficacy with manageable toxicity in pts with HER2+ MBC with brain mets

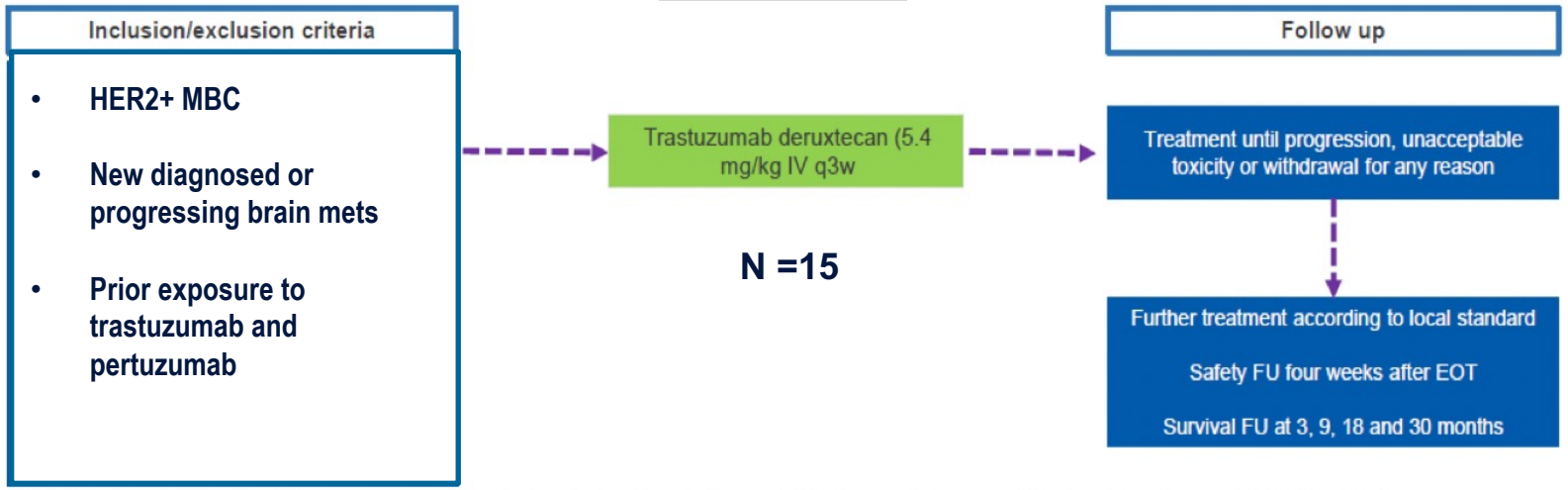
@ErikaHamilton9

SARAH CANNON

Vaz Batista M et al. SABCS 2021

TUXEDO-1: T-DXd in pts with HER2+ BC & active brain mets

Study schema



BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.
EudraCT: 2020-000981-41.

Primary Endpoint: ORR (CNS) by RANO-BM criteria

Secondary Endpoints:

- Clinical Benefit Rate (CR+PR+SD ≥6 months)
- Extracranial Response rate
- PFS
- OS
- Safety
- Quality of Life

Patient population (n=15)

Visceral mets	**80%**
Progressive brain mets*	**60%**
Untreated brain mets	**40%**
Prior T-DM1	**60%**
Prior lapatinib	**26.7%**

* After local therapy

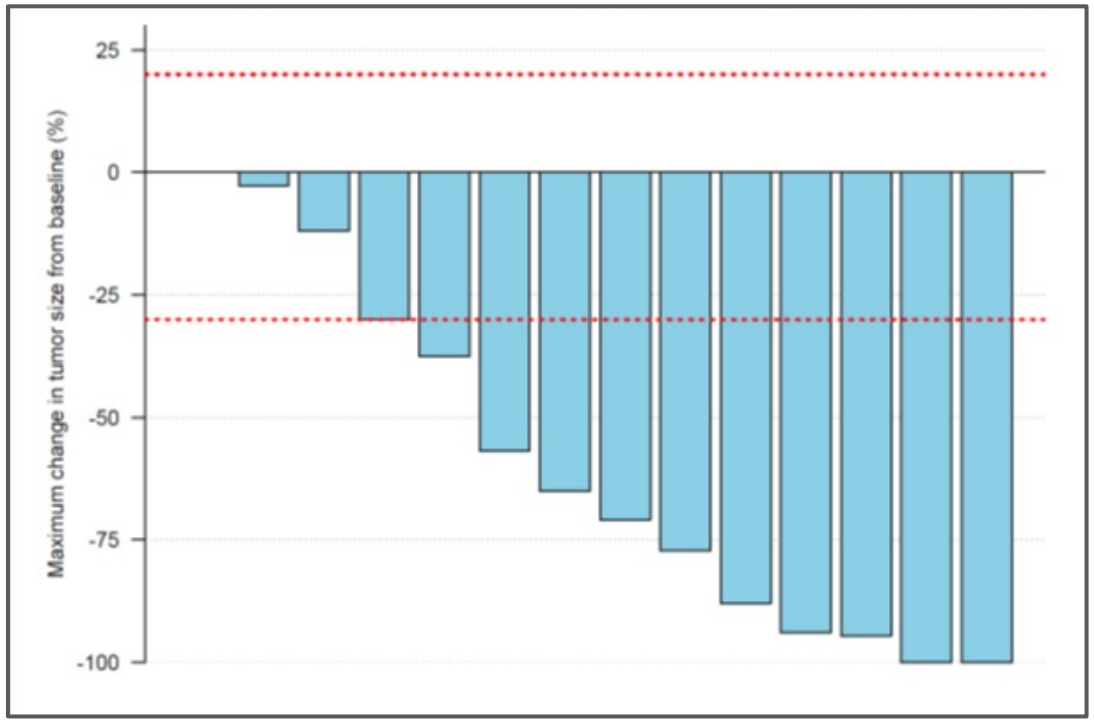
@ErikaHamilton9

SARAH CANNON

Bartsch R et al. ESMO Breast 2022

TUXEDO: Efficacy endpoints

ORR by RANO-BM criteria (Primary EP)



ORR (ITT population; *n*=15): 73.3% (95% CI 48.1-89.1)

Secondary Endpoints

Median follow-up: 11 months (range 3 – 17 months)

1. **PFS: 14 months (95% CI 11.0-n.r.)**

2. **CBR*: 86.7% (13/15) in ITT**
   CBR: 92.9% (13/14) in PP**

3. **Extracranial response rate:**
   Pts. with extracranial metastases at BL (*n*=13):
   PR 5/13 (27.8%)
   Pts with measurable extracranial disease at BL (*n*=8):
   PR 5/8 (62.5%)

4. **Median OS: Not reached**

- Study met primary EP
- No new safety signals reported (EF decrease G3 in 1 pt; ILD G2 in 1 pt)
- QoL maintained during treatment duration

* CR+PR+SD ≥6 months
** Per protocol population

@ErikaHamilton9

SARAH CANNON

Bartsch R et al. ESMO Breast 2022

Select ongoing trials in HER2+ BC w/ brain mets

- DESTINY Breast 07: Evaluating T-DXd and T-DXd + Tucatinib in pts with active brain mets (NCT04538742)
- DESTINY Breast-12: T-DXd in pretreated HER2+ MBC patients w/ or w/o brain mets (NCT04739761)
- GDC-0084 (dual PI3K/mTOR inhibitor) +Trastuzumab for pts with HER2+ BC brain mets (NCT03765983)
- HER2-CAR T cells for pts with brain or leptomeningeal mets from HER2+ BC (NCT03696030)
- Dendritic cell vaccines against HER2/HER3 + pembrolizumab for pts with HER2+ BC & brain mets (NCT04348747)

Thank You

SARAH CANNON