Updates in Breast Medical Oncology: 2023

Carey K. Anders, MD

Professor of Medicine

Medical Director of the DCBSM; Division Chief

NCOA Meeting 8/2023

DukeHealth

Disclosures

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

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

- Royalties: UpToDate, Jones and Bartlett
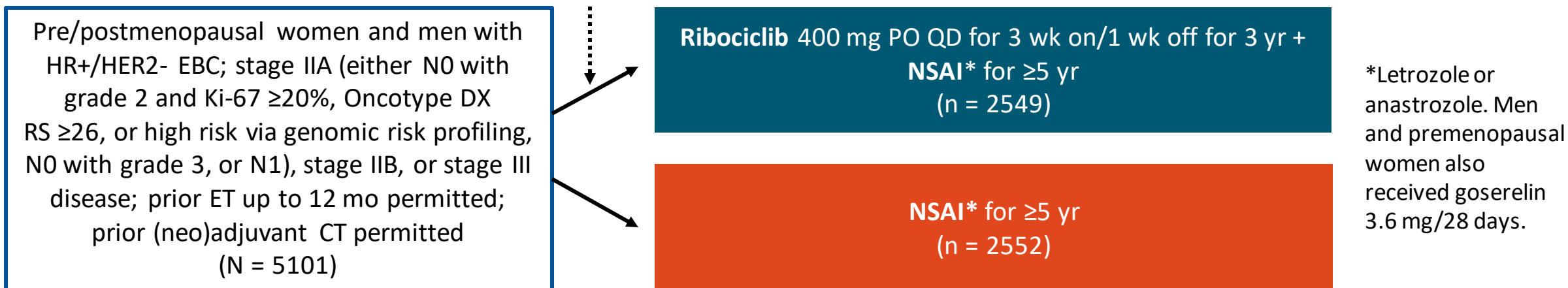
Updates in Early Stage Breast Cancer:

NATALEE
MONARCHE: Subgroup Age Analysis

- International, randomized, open-label phase III trial (data cutoff: January 11, 2023; median f/u: 34.0 mo with minimum of 21 mo)

Stratified by stage (II vs III), menopausal status (men and premenopausal vs postmenopausal women), prior (neo)adjuvant CT (yes vs no), geography (N America/W Europe/Oceania vs rest of world)

Pre/postmenopausal women and men with HR+/HER2- EBC; stage IIA (either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1), stage IIB, or stage III disease; prior ET up to 12 mo permitted; prior (neo)adjuvant CT permitted (N = 5101)

Ribociclib 400 mg PO QD for 3 wk on/1 wk off for 3 yr + **NSAI*** for ≥5 yr (n = 2549)

NSAI* for ≥5 yr (n = 2552)

*Letrozole or anastrozole. Men and premenopausal women also received goserelin 3.6 mg/28 days.

Primary endpoint: iDFS (STEEP criteria)

- ~85% power assuming hazard ratio of 0.76 (1-sided α = 0.025), with 2 interim efficacy analyses planned (at ~350 and ~425 events) plus final analysis (~500 events)

Key secondary endpoints: recurrence-free survival, DDFS, OS, PROs, PK, safety

Slamon. ASCO 2023. Abstr LBA500. NCT03701334.

NATALEE: Baseline Characteristics

Characteristic, n (%)	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Median age, yr (range)	52 (24-90)	52 (24-89)
Postmenopausal women	1423 (56)	1420 (56)
ECOG PS 0	2106 (83)	2132 (84)
Anatomic stage		
▪ IIA	479 (19)	521 (20)
▪ IIB	532 (21)	513 (20)
▪ III	1528 (60)	1512 (59)
Nodal status at dx		
▪ NX	272 (11)	264 (10)
▪ N0	694 (27)	737 (29)
▪ N1	1050 (41)	1049 (41)
▪ N2/N3	483 (19)	467 (18)
Prior ET	1824 (72)	1801 (71)
Prior (neo)adjuvant CT	2249 (88)	2245 (88)

NATALEE: Second Interim Efficacy Analysis of iDFS (Primary Endpoint)

iDFS Outcome	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Events, n (%)	189 (7.4)	237 (9.3)
3-yr rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906; *P* = .0014)	

- NATALEE met its primary endpoint, with ribociclib + NSAI significantly improving iDFS vs NSAI alone
  - *P* value of .0014 met protocol-defined stopping boundary for superior efficacy (1-sided *P* <.0128)

- iDFS improvement generally consistent across prespecified patient subgroups

- With ribociclib + NSAI vs NSAI alone:
  - Absolute iDFS benefit at 3 yr: 3.3%
  - Risk of invasive disease decreased by 25.2%
- Ongoing patients to continue receiving tx, with follow-up to continue

*** At time of analysis, 78% in ribo group and 72% in placebo group, still on treatment.....

NATALEE: DDFS and OS

DDFS* Outcome	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Events, n (%)	167 (6.6)	212 (8.3)
3-yr rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905; *P* = .0017)	

OS Outcome	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Events, n (%)	61 (2.4)	73 (2.9)
HR (95% CI)	0.759 (0.539-1.068; *P* = .0563)	

- With ribociclib + NSAI vs NSAI alone:
  - Absolute DDFS benefit at 3 yr: 2.2%
  - Risk of distant disease decreased by 26.1%

- Nonsignificant trend toward improved OS observed with ribociclib + NSAI vs NSAI alone
  - Further follow-up for OS planned

NATALEE: Safety

AEs (%)	Ribociclib + NSAI (n = 2524)		NSAI Alone (n = 2444)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AEs of special interest				
Neutropenia	62.1	43.8	4.5	0.8
▪ Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs	25.4	8.3	10.6	1.5
QT interval prolongation	5.2	1.0	1.2	0.5
▪ ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis	1.5	0	0.8	0.1
Other clinically relevant AEs				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- **Ribociclib discontinued due to AE in 19%** of patients, with most discontinuations early in tx (median: 4 mo)
  - For NSAI alone arm, NSAI discontinued due to AE in 4% of patients

- With ribociclib + NSAI vs NSAI alone:
  - Most common any-grade AEs leading to discontinuation were liver related (8.9% vs 0.1%) or arthralgia (1.3% vs 1.9%)
  - New QTcF interval >500 ms: 0.1% vs <0.1% (increase from BL of >60 ms: 0.8% vs 0.1%)

- **Ribociclib 400 mg had lower rates of dose-dependent toxicities** vs pooled analysis of MONALEESA trials using ribociclib 600 mg
  - Neutropenia: 62% vs 74%
  - ECG QT prolongation: 4.2% vs 6.5% (grade ≥3: 0.2% vs 1.2%)

Slamon. ASCO 2023. Abstr LBA500.

Practical Considerations:
Can we start using ribociclib in the adjuvant space?

- 25% risk reduction is clinically meaningful → absolute benefit (3.3%) is modest, but only 20% of patients having completed 3 yr of therapy
    - Unknown if benefit will persist over time, but in monarchE, benefits increased with time
    - Can only be given with AI; for the ~20% of patients who d/c AI therapy, they are unable to continue on ribociclib with tamoxifen
- Must weight benefits vs risks → 3 yr of therapy
    - 8.3% of patients had grade ≥3 liver AEs, which requires holding drug
- For now, given longer f/u in monarchE, abemaciclib should likely be the standard for high-risk HR+ EBC
    - Consider ribociclib in patients with high genomic risk who missed monarchE eligibility but were eligible for NATALEE
    - Ribociclib could also be an option for those intolerant of abemaciclib

Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial

Prof Stephen R D Johnston, MD • Masakazu Toi, MD • Joyce O'Shaughnessy, MD • Priya Rastogi, MD • Prof Mario Campone, MD • Prof Patrick Neven, MD • et al. Show all authors • Show footnotes

THE LANCET Oncology

- Phase III monarchE trial demonstrated that adjuvant abemaciclib for 2 years + ET significantly improved iDFS vs ET alone in patients with HR+/HER2- EBC that is node positive and at high risk of recurrence
  - 2-yr iDFS rate: 92.2% vs 88.7% (hazard ratio: 0.75; 95% CI: 0.60-0.93; P = .01)

- Results from monarchE led to FDA approval of abemaciclib in combination with ET (tamoxifen or AI) for adjuvant treatment of adults with HR+/HER2- EBC that is node positive and at high risk of recurrence
  - Ki-67 score requirement from original approval dropped from label in March 2023

1. Johnston. JCO. 2020;38:3987. 2. Johnston. Lancet Oncol. 2023;24:77. 3. Abemaciclib PI. 4. Acuña-Villaorduña. Am Soc Clin Oncol Educ Book. 2023;43:e389838. 5. Sedrak. CA Cancer J Clin. 2021;71:78. 6. Hamilton. ASCO 2023. Abstr 501.

MonarchE Subgroup Analysis by Age: Study Design

- International, randomized, open-label phase III trial

Women or men with high-risk, node-positive, HR+/HER2- EBC; prior (neo)adjuvant CT permitted; pre- or postmenopausal; no distant metastasis; ≤16 mo from surgery to randomization; ≤12 wk of ET after last non-ET
(N = 5637)

ITT Population (Cohorts 1 + 2)

Cohort 1 (91% of patients)
≥4 positive ALNs *or* 1-3 positive ALNs plus histologic grade 3 and/or tumor ≥5 cm

Cohort 2 (9% of patients)
1-3 positive ALNs, Ki-67 ≥20% per central testing, grade 1-2, tumor size <5 cm

Stratified by prior CT, menopausal status, region

Abemaciclib 150 mg BID up to 2 yr + **ET** per standard of care of physician's choice for 5-10 yr as clinically indicated
(n = 2808)

ET per standard of care of physician's choice for 5-10 yr as clinically indicated
(n = 2829)

Primary endpoint: iDFS

Key secondary endpoints: iDFS in Ki-67 high (≥20%) population, DRFS, OS, safety, PROs, PK

Current analysis compares efficacy, safety, and PROs in patients aged <65 vs ≥65 yr

Percentage of patients aged ≥75 yr: 3%

Hamilton. ASCO 2023. Abstr 501. Johnston. Lancet Oncol. 2023;24:77.

NATALEE and monarchE: Patient population now eligible for adjuvant CDK 4/6i

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IA	T1N0		
Stage IB	T0N1mi		
	T1N1mi		G3 or Ki67 $\geq$ 20%
Stage IIA	T0N1		
	T1N1		G3 or Ki67 $\geq$ 20%
	T2N0	G3, or G2 with Ki-67 $\geq$ 20% or high genomic risk[c]	
Stage IIB	T2N1		G3 or Ki67 $\geq$ 20%
	T3N0		
Stage IIIA	T0N2		
	T1N2		
	T2N2		
	T3N1		
	T3N2		
Stage IIIB	T4N0		
	T4N1		
	T4N2		
Stage IIIC	Any TN3		

- Pre- and postmenopausal women
- Men

Choice of therapy will depend on approval, access, risk, long-term efficacy, safety profile, and patient preference

Not to forget: **gBRCA testing** in patients eligible for olaparib (OlympiA)

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement;; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ... RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm bu less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growin... ...reast cancer. [a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3). [b] Capped at 40% ($\approx$ 2000 patients). Simplified inclusion criteria are used in the illustration. [c] High risk as determined by Oncotype DX, P... ...clin Risk Score.

References: 1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(suppl 15) [abs... ...E011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020; [5]https://clinicaltrials.gov/ct2/show/NCT03155997

KNOWLEDGE CONQUERS CANCER

monarchE Subgroup Analysis by Age: Baseline Characteristics

Characteristic, %	All (N = 5637)	Age <65 Yr (n = 4787)	Age ≥65 Yr* (n = 850)
Pathologic tumor size			
▪ <20 mm	27	28	23
▪ 20 to <50 mm	50	48	57
▪ ≥50 mm	22	22	19
No. positive LN*			
▪ 1-3	40	41	36
▪ ≥4	60	59	64
Histopathologic grade			
▪ G1	8	8	7
▪ G2	49	49	52
▪ G3	38	38	37
Prior (neo)adjuvant CT	94	97	82
ECOG PS† 0/1	85/15	86/14	77/23

Trial inadvertently enrolled *14 patients with 0 positive LN and †3 patients with ECOG PS >1.

Characteristic, %	Treated Patients		
	All (n = 5591)	Age < 65 Yr (n = 4751)	Age ≥65 Yr (n = 840)
No. preexisting comorbidities			
▪ 0	17	19	6
▪ 1-3	48	48	44
▪ ≥4	35	33	51
Initial ET			
▪ AI	68	64	95
▪ Tamoxifen	31	36	5

Values may not add up to 100% due to rounding or missing data.

- Patients aged ≥65 yr had higher baseline ECOG PS, more comorbidities, and lower rates of prior (neo)adjuvant CT

Hamilton. ASCO 2023. Abstr 501.

monarchE Subgroup Analysis by Age: iDFS and DRFS

Outcome	iDFS			DRFS		
	ITT	Age <65 Yr	Age ≥65 Yr	ITT	Age <65 Yr	Age ≥65 Yr
Events, n/N						
▪ Abemaciclib + ET	336/2808	270/2371	66/437	281/2808	230/2371	51/437
▪ ET alone	499/2829	414/2416	85/413	421/2829	353/2416	68/413
Hazard ratio (95% CI)	0.664 (0.578-0.762)	0.646 (0.554-0.753)*	0.767 (0.556-1.059)*	0.659 (0.567-0.767)	0.647 (0.548-0.764)†	0.748 (0.520-1.077)†
4-yr rate, %						
▪ Abemaciclib + ET	85.8	86.5	82.0	88.4	88.8	86.1
▪ ET alone	79.4	79.8	76.8	82.5	82.6	81.5
Absolute benefit in 4-yr rate, %	6.4	6.7	5.2	5.9	6.2	4.6

Interaction *P* value of *.35 and †.49

- Benefits with abemaciclib + ET were comparable between ITT population and those aged ≥65 yr
  - Results were consistent in cohort 1

Hamilton. ASCO 2023. Abstr 501.

monarchE Subgroup Analysis by Age: AEs

AE	Grade	Abemaciclib + ET		
		All (n = 2791)	Age <65 Yr (n = 2361)	Age ≥65 Yr (n = 430)
Any AE	▪ Any	98	98	99
	▪ ≥3	50	49	54
Diarrhea	▪ 1	45	46	37
	▪ 2	31	31	30
	▪ 3	8	7	12
Fatigue	▪ 1	23	23	21
	▪ 2	15	14	20
	▪ 3	3	2	6
Neutropenia	▪ 1/2	26	27	22
	▪ ≥3	20	20	19
ALT increase	▪ 1/2	10	10	7
	▪ ≥3	3	3	3
VTE	▪ Any	3	2	3
	▪ ≥3	1	1	1
ILD	▪ Any	3	3	3
	▪ ≥3	<1	<1	<1

Summary:

Slight numerical increase in grade 3 diarrhea:
12% vs. 7%

Slight numerical increase in grade 2-3 fatigue:
grade 2: 20% vs 14%
grade 3: 6% vs. 2%

Neutropenia, LFTs changes, VTE and ILD all similar
By Age

Hamilton. ASCO 2023. Abstr 501.

monarchE Subgroup Analysis by Age: Dose Adjustments and QoL

Abemaciclib Dose Adjustment due to AE, %	Abemaciclib + ET		
	All (N = 2791)	Age <65 Yr (n = 2361)	Age ≥65 Yr (n = 430)
Interruptions	62	60	68
Reductions	44	42	55
Discontinuations	18	15	38
▪ No prior dose reductions	10	8	19

- Patients aged ≥65 yr had more frequent abemaciclib dose adjustments
  - More dose adjustments, discontinuations due to AEs in those aged ≥75 yr
- Comparable QoL per FACT-B total score between age subgroups and treatment arms

- 4-yr iDFS rates comparable across 3 equal-sized subgroups classified by relative dose intensity of abemaciclib
  - RDI: 0-66%; 66-93%; ≥93%
  - 4-yr iDFS by lowest to highest relative dose intensity: 87.1% vs 86.4% vs 83.7%
  - Similar results observed in cohort 1

monarchE Subgroup Analysis by Age: Investigators' Conclusions

- In this subgroup analysis of monarchE by age, consistent iDFS and DRFS benefits with adjuvant abemaciclib + ET vs ET alone were observed in patients with high-risk HR+/HER2- EBC who were aged <65 vs ≥65 yr

- At baseline, high ECOG PS and medical comorbidities were more common in older patients

- AE rates and QoL similar between age subgroups
  - Dose reductions, treatment discontinuations more common in older patients
  - iDFS benefit similar across evaluated abemaciclib relative dose intensity categories

- Investigators concluded that results support use of adjuvant abemaciclib across different ages
  - Recommend counseling patients about treatment expectations and further counseling for older patients about symptom management and close monitoring for AEs needing dose modification

Hamilton. ASCO 2023. Abstr 501.

Updates in Metastatic Breast Cancer:

TROPICS—02 OS update
Patritumab Deruxtecan
SONIA
PALMIRA

Sacituzumab Govitecan: Trop-2–Targeted ADC

- Trop-2 is expressed in all breast cancer subtypes and is associated with poor prognosis

  FDA approved in BC for:

  Unresectable locally advanced or metastatic TNBC with ≥2 prior systemic tx (≥1 for metastatic disease)

  Unresectable locally advanced or metastatic HR+/HER2-* BC with prior ET and ≥2 additional systemic tx in metastatic setting

Humanized Anti–Trop-2 Antibody
- Targets Trop-2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ

SN-38 Payload
- Delivers up to 136-fold more SN-38 to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor
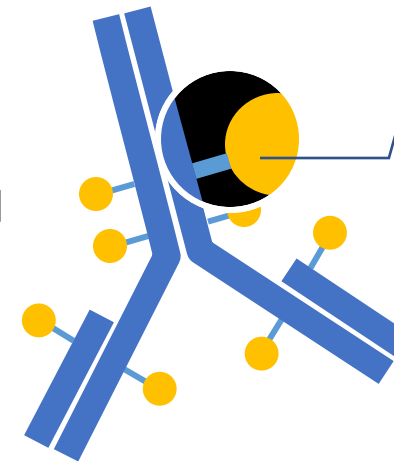
Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Goldenberg. Oncotarget. 2015;6:22496. Khoury. ASCO 2019. Abstr e14651.
Ambrogi. PLoS One. 2014;9:e96993. Vidula. ASCO 2017. Abstr 1075.
Sacituzumab govitecan PI. Tagawa. ASCO 2019. Abstr TPS3153.
Bardia. JCO. 2017;35:2141. Goldenberg. MAbs. 2019;11:987.
Sharkey. Clin Cancer Res. 2015;21:5131.

TROPiCS-02: Sacituzumab Govitecan vs CT for Previously Treated HR+/HER2- ABC—Final OS Analysis

- Randomized, multicenter, open-label phase III study (data cutoff: Dec 1, 2022)

Stratification by visceral metastases (yes or no), ET in metastatic setting   *prior CT lines (2 or 3-4)*

Patients with locally recurrent or metastatic, inoperable HR+/HER2-* breast cancer with PD after ≥1 ET, taxane, and CDK4/6 inhibitor in any setting; 2-4 prior lines of CT for MBC; measurable disease by RECIST v1.1
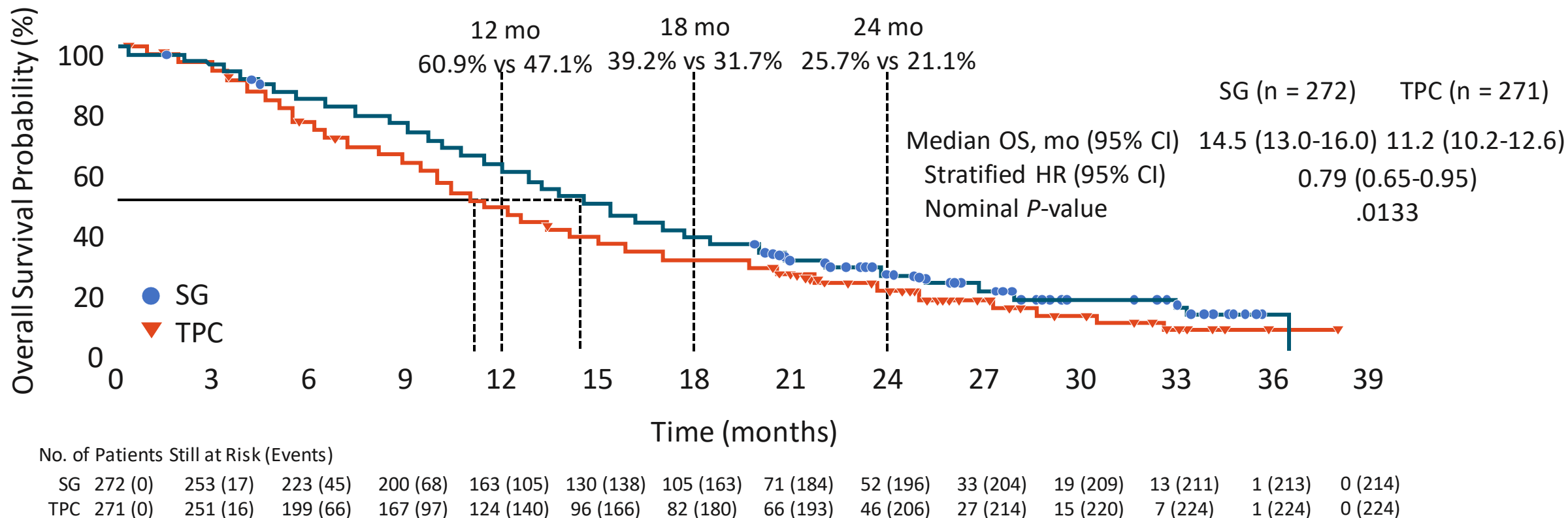(N = 543)

Sacituzumab Govitecan
10 mg/kg IV Day 1, Day 8 Q3W
(n = 272)

Physician's Choice of Treatment†
(n = 271)
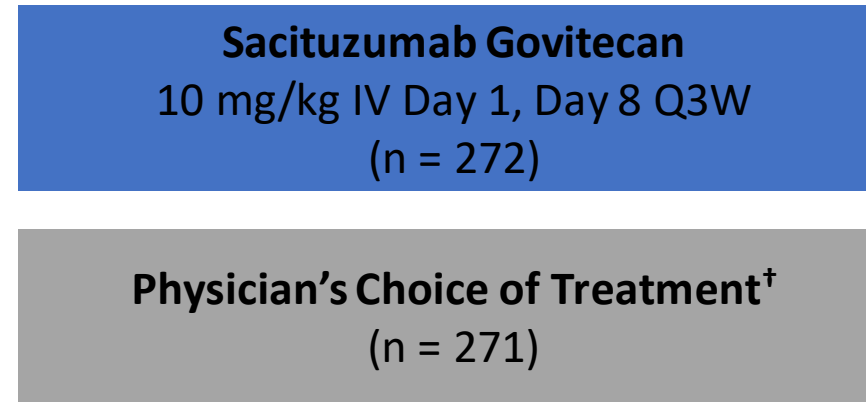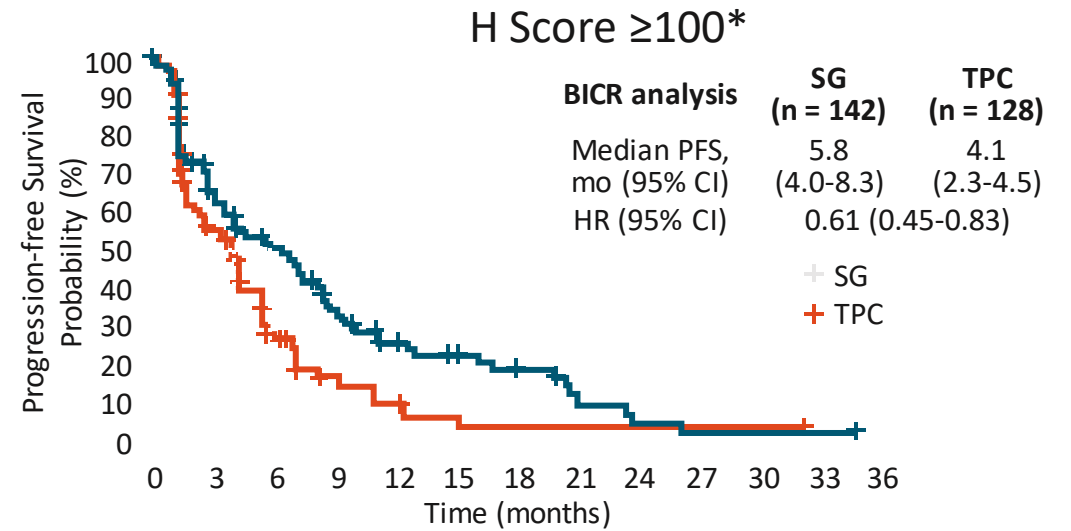
Until PD or unacceptable toxicity
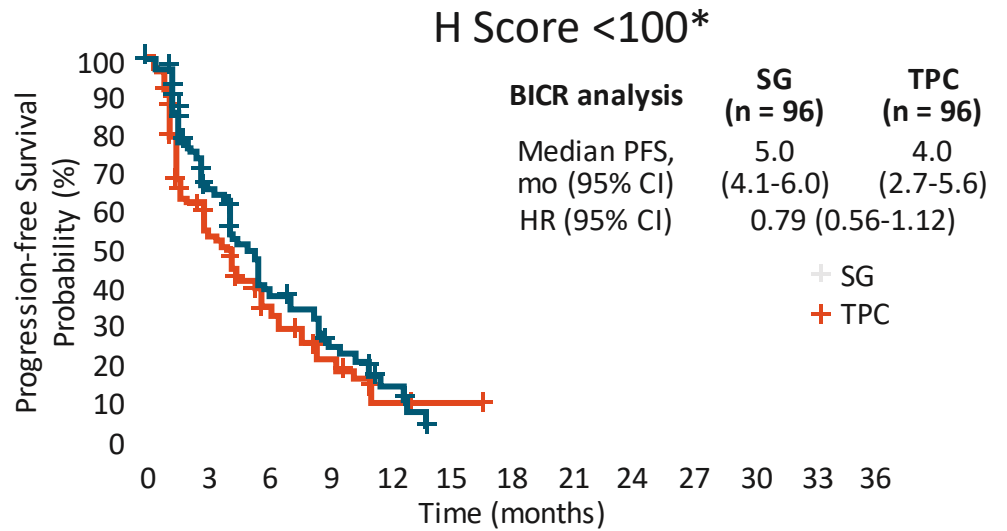
Primary endpoint: PFS (by BICR)

Secondary endpoints: OS, ORR, DoR, CBR (by LIR and BICR); PROs; safety

Exploratory endpoint: OS by HER2 IHC status

Tolaney. ASCO 2023. Abstr 1003.

TROPiCS-02: Updated OS

12 mo
60.9% vs 47.1%

18 mo
39.2% vs 31.7%

24 mo
25.7% vs 21.1%

	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	0.79 (0.65-0.95)	
Nominal *P*-value	.0133	

Overall Survival Probability (%)

Time (months)

No. of Patients Still at Risk (Events)

| SG | 272 (0) | 253 (17) | 223 (45) | 200 (68) | 163 (105) | 130 (138) | 105 (163) | 71 (184) | 52 (196) | 33 (204) | 19 (209) | 13 (211) | 1 (213) | 0 (214) |
| TPC | 271 (0) | 251 (16) | 199 (66) | 167 (97) | 124 (140) | 96 (166) | 82 (180) | 66 (193) | 46 (206) | 27 (214) | 15 (220) | 7 (224) | 1 (224) | 0 (224) |

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TROPiCS-02: PFS and OS by Trop-2 Expression Level

H Score <100*

BICR analysis	SG (n = 96)	TPC (n = 96)
Median PFS, mo (95% CI)	5.0 (4.1-6.0)	4.0 (2.7-5.6)
HR (95% CI)	0.79 (0.56-1.12)	

	SG (n = 96)	TPC (n = 96)
Median OS, mo (95% CI)	14.9 (12.7-18.1)	11.3 (10.0-13.3)
HR (95% CI)	0.78 (0.57-1.06)	

H Score ≥100*

BICR analysis	SG (n = 142)	TPC (n = 128)
Median PFS, mo (95% CI)	5.8 (4.0-8.3)	4.1 (2.3-4.5)
HR (95% CI)	0.61 (0.45-0.83)	

	SG (n = 142)	TPC (n = 128)
Median OS, mo (95% CI)	14.4 (12.7-17.0)	11.2 (9.9-12.7)
HR (95% CI)	0.82 (0.63-1.08)	
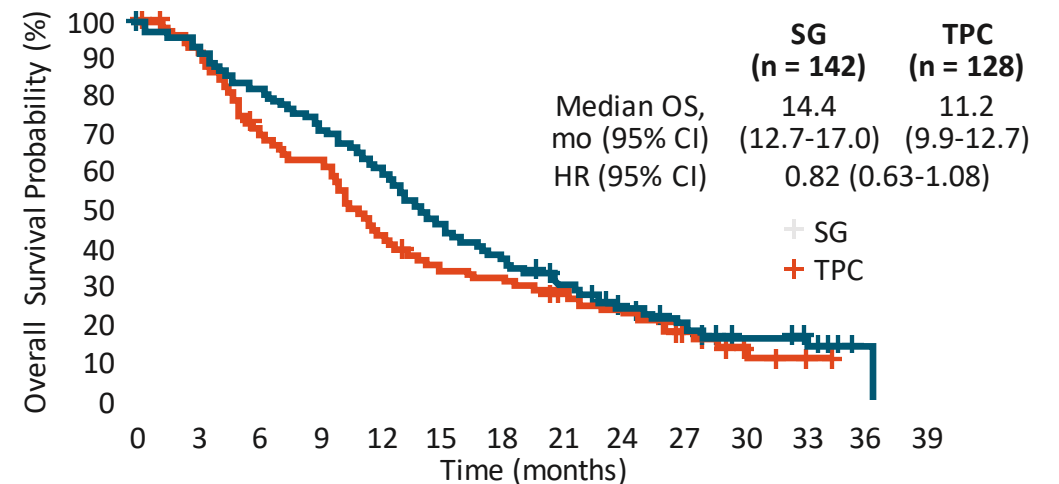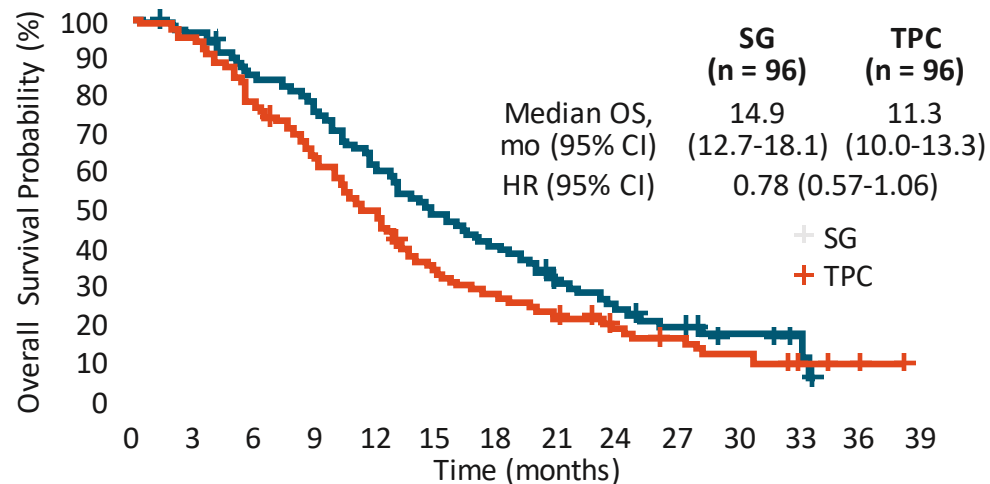
*H score <100: 42% of patients; HR ≥100: 58% of patients.

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Patritumab Deruxtecan (U3-1402): HER3-DXd

Human anti-HER3 IgG1 mAb

Linker and payload

DXd Payload MoA: topoisomerase I inhibitor

High potency, membrane-permeable payload with short systemic half-life

High drug:antibody ratio: ~8:1

Stable linker-payload

Tumor-selectable cleavable linker

Bystander killing effect

Cys

Cleavable tetrapeptide-based linker

■ Cysteine residue
● Deruxtecan

Conjugation chemistry:
Drug-linker conjugated to cysteine residues of mAb

Payload (DXd)
Exatecan derivative

Yu. WCLC 2020. Abstr OA03.04. Hashimoto. Clin Cancer Res. 2019;25:7151.

HER3-DXd in HER2-Negative MBC: Study Design

- Multicenter, 3-part, open-label phase II trial; data for Part A reported

Patients with HER2- locally advanced or MBC; 1 prior CDK4/6i, ≤2 prior CT, and unlimited ET regimens for HR+ BC, or 1-3 prior CT regimens for TNBC; no prior anti-HER3 agents or exatecan-based ADCs (N = 60)

Patritumab deruxtecan 5.6 mg/kg IV Q3W

Part B

Expansion in up to 3 populations based on combinations of HER3 (25%-74% or ≥75%) and ER (negative, 1%-10% or >10%) expression levels (N = 20-40)

Patritumab deruxtecan 5.6 mg/kg IV Q3W

Part Z

Patients with HER2+ MBC after prior T-DXd (N = 21)

Patritumab deruxtecan 5.6 mg/kg IV Q3W

Primary endpoints: ORR, 6-mo PFS in HER2- MBC

Secondary endpoints: DoR, CBR, PFS in HER2+ and HER2- MBC; safety

Hamilton. ASCO 2023. Abstr 1004.

HER3-DXd in HER2- MBC: Response by HER3 Expression

Investigator-Assessed Response, n (%)	HER3 ≥75% (n = 30)	HER3 25%-74% (n = 13)	HER3 <25% (n = 4)	Unknown HER3 (n = 13)	Total (N = 60)
Best overall response					
▪ CR	0	0	0	0	0
▪ PR	10 (33.3)	6 (46.2)	2 (50.0)	3 (23.1)	21 (35.0)
▪ SD	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
▪ PD	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
▪ Missing	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR	10 (33.3)	6 (46.2)	2 (50.0)	3 (23.1)	21 (35.0)
CBR	12 (40.0)	7 (53.8)	2 (50.0)	5 (38.5)	26 (43.3)
DoR ≥6 mo (% of responders)	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

Hamilton. ASCO 2023. Abstr 1004.

HER3-DXd in HER2-Negative MBC: Safety and Dosing

TRAEs Occurring in ≥10%, n (%)	Patients (N = 60)	
	Any Grade	Grade 3/4
Any	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased appetite	8 (13.3)	0
Neutrophil count decreased*	7 (11.7)	3 (5.0)
WBC count decreased*	7 (11.7)	1 (1.7)

*More than 1 TRAE could be reported per patient. †Adjudication of interstitial lung disease/pneumonitis events ongoing at data cutoff. ‡All due to AE: GI (n = 4); thrombocytopenia (n = 2); fatigue, dyspnea, pruritus (n = 1 each).

SAEs, n (%)	Patients (N = 60)
Treatment related	
▪ Interstitial lung disease†	1 (1.7)
▪ Nausea/vomiting	1 (1.7)
▪ Pneumonitis	1 (1.7)
▪ Thrombocytopenia	1 (1.7)
Unrelated	
▪ Dyspnea	1 (1.7)
▪ *Pneumocystis jirovecii* pneumonia	1 (1.7)
▪ Pneumothorax	1 (1.7)

Supports activity of patritumab deruxtecan into treatment landscape across MBC subtypes:

Part B (HER2- expansion cohort) and Part Z (HER2 positive after progression on T-DXd) of the phase II trial currently enrolling patients regardless of HER3 expression

Hamilton. ASCO 2023. Abstr 1004.

SONIA: Study Design

- Investigator-initiated, randomized phase III trial

Stratified by CDK4/6i, visceral disease, and prior (neo)adjuvant endocrine therapy

Patients with HR+/HER2- ABC; no prior therapy for ABC; neoadjuvant therapy allowed if disease-free interval >12 mo after nonsteroidal AI; no visceral crisis
(N = 1050)

| Nonsteroidal AI + CDK4/6i (n = 524) | Fulvestrant |
| Nonsteroidal AI (n = 526) | Fulvestrant + CDK4/6i |

Primary endpoint: PFS2 (time from randomization to second disease progression or death) per RECIST V1.1

Planned primary analysis after 574 PFS2 events; 89% power to detect superiority with 2-sided α = 5%

Secondary endpoints: OS, QoL, cost-effectiveness

Sonke. ASCO 2023. Abstr LBA1000.

SONIA: Baseline Characteristics

Characteristic, n (%)	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Median age, yr (range)	64 (24-88)	63 (25-87)
WHO PS		
0	257 (49)	257 (49)
≥1	267 (51)	269 (51)
Menopausal status		
Pre/peri	69 (13)	76 (14)
Post	455 (87)	450 (86)
Disease-free interval		
Newly diagnosed	182 (35)	182 (35)
≤24 mo	96 (18)	98 (19)
>24 mo	246 (47)	246 (47)

Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Prior (neo)adjuvant tx		
CT	212 (40)	210 (40)
ET	258 (49)	254 (48)
Metastatic site		
Visceral	291 (56)	292 (56)
Bone only	91 (17)	91 (17)
Measurable disease	315 (60)	312 (59)
CDK4/6 inhibitor		
Pabociclib	479 (91)	479 (91)
Ribociclib	42 (8)	44 (8)
Abemaciclib	3 (1)	3 (1)

SONIA: PFS1

Characteristic	AI + CDK4/6i (n = 524)	AI (n = 526)
Events, n	310	407
Median PFS1, mo	24.7	16.1
Hazard ratio (95% CI)	0.59 (0.51-0.69)	
2-sided P value	<.0001	

No. at Risk

524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (214)
526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)
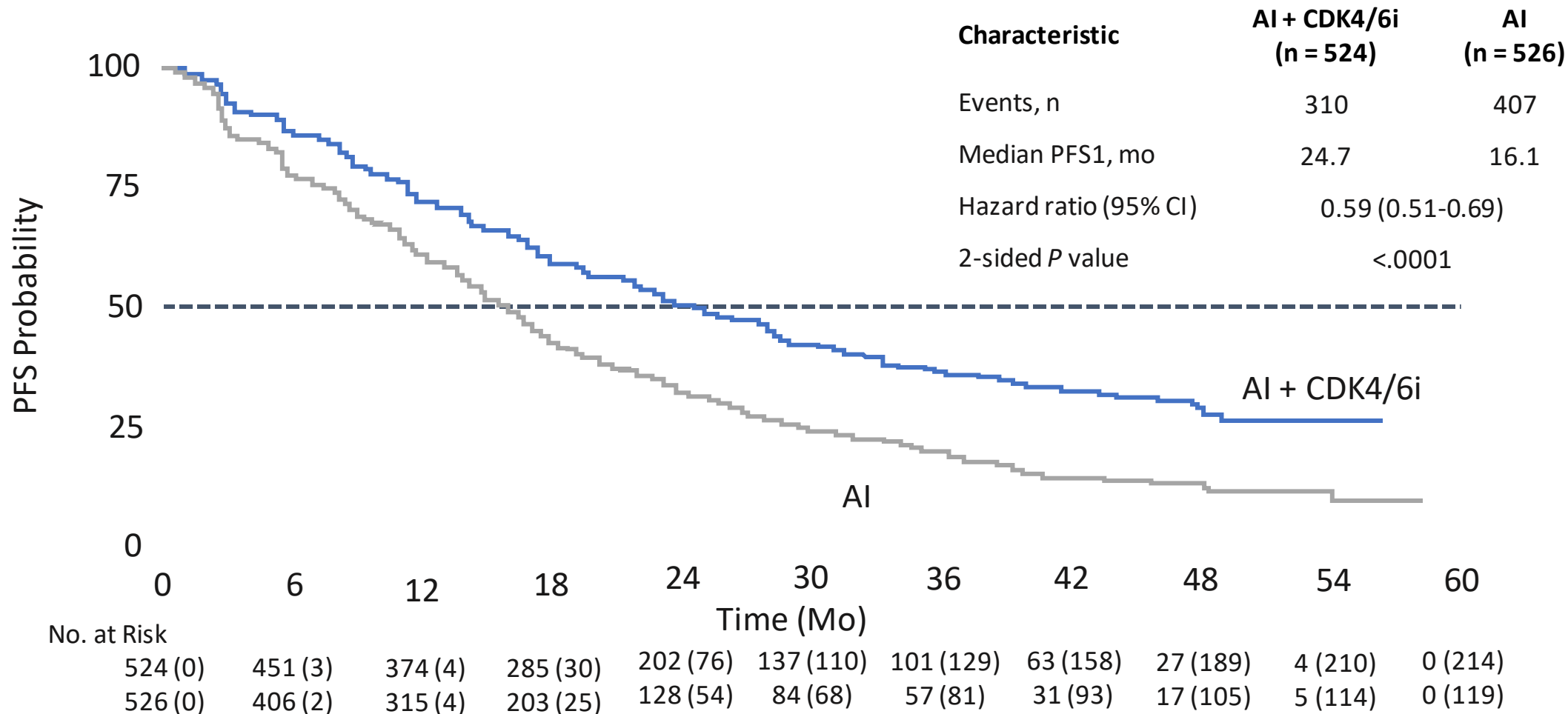
Median follow up: 37.3 mo

Sonke. ASCO 2023. Abstr LBA1000. Reproduced with permission.

SONIA: PFS2 (Primary Endpoint)

Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Events, n	281	310
Median PFS2, mo	31.0	26.8
Hazard ratio (95% CI)	0.87 (0.74-1.03)	
2-sided *P* value	.10	

First-line CDK4/6i

Second-line CDK4/6i

No. at Risk

524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (215)	5 (239)	0 (243)
526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)

SONIA: Overall Survival

PFS Probability (y-axis): 0, 25, 50, 75, 100

Time (Mo) (x-axis): 0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60

First-line CDK4/6i

Second-line CDK4/6i

Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Events, n	184	188
Median OS, mo	45.9	53.7
Hazard ratio (95% CI)	0.98 (0.80-1.20)	
2- sided *P* value	.83	

No. at Risk

524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

Practical Considerations:
Can Specific Patients Delay CDK4/6 Inhibitor Therapy?

Key remaining questions

- **Optimal 2L therapy?** Fulvestrant alone not currently SoC as typically combined with other targeted therapies (i.e. mTOR and often another CDK4/6i)

- **Does the CDK4/6 inhibitor matter?** >90% treated with palbociclib
  - OS data positive for ribociclib and abemaciclib, but not palbociclib

Who are the patients with very good risk who can delay CDK4/6 inhibitor therapy?

- Are there genomic and/or clinical predictors?

- For now, delaying CDK4/6 inhibitor therapy can be considered in older, frail patients....clinical judgement will be critical here....

PALMIRA: Study Design

- International, randomized, open-label trial conducted in Europe
  (data cutoff: February 2, 2023; median follow-up: 13.2 mo [range: 0-41.1])

*Stratified by prior ET (fulvestrant vs AI);
site of disease (visceral vs nonvisceral)*

Women with HR+/HER2- ABC;
premenopausal with ovarian suppression
or postmenopausal; PD on 1L palbociclib +
ET (AI or fulvestrant) after clinical benefit
or PD on palbociclib-based adjuvant tx
after ≥12 mo of tx within 12 mo of
completion; measurable disease;
ECOG PS 0/1
(N = 198)

2:1

Palbociclib 75-125 mg PO QD for 3 wk on/1 wk off +
ET*
(n = 136)

ET*
(n = 62)

*Until PD,
unacceptable
toxicity, or study
withdrawal*

*Depending on prior agent, either fulvestrant 500 mg IM on
D1/15/29 and QM thereafter or letrozole 2.5 mg PO QD.

Primary endpoint: PFS per RECIST v1.1 by investigator

Trial has 80% power to detect mPFS increase of 2.74 mo over 4 mo with ET (2-sided α = 0.05; hazard ratio: 0.59)

Secondary endpoints: ORR, CBR, OS, DoR, TTR, time to progression, QoL, safety and tolerability

NCT03809988. Llombart-Cussac. ASCO 2023. Abstr 1001.

PALMIRA: Baseline Characteristics and Patient Disposition

Characteristic	Palbociclib + ET (n = 136)	ET (n = 62)
Median age, yr (range)	59 (33-85)	61 (34-83)
Postmenopausal, n (%)	118 (86.8)	56 (90.3)
ECOG PS 1, n (%)	45 (33.1)	31 (50.0)
Measurable disease at BL, n (%)	94 (69.1)	44 (71.0)
Visceral involvement, n (%)	84 (61.8)	37 (59.7)
<3/≥3 metastatic sites, n (%)	92 (67.6)/44 (32.4)	38 (61.3)/24 (38.7)
Prior ET, n (%)		
▪ Fulvestrant	16 (11.8)	4 (6.5)
▪ AI	120 (88.2)	58 (93.5)
Duration of 1L palbociclib, n (%)		
▪ 6-12 mo	18 (13.2)	10 (16.1)
▪ ≥12 mo	118 (86.8)	52 (83.9)
Last dose of 1L palbociclib, n (%)		
▪ 125 mg	83 (53.2)	33 (61.0)
▪ 100 mg	45 (43.5)	27 (33.1)
▪ 75 mg	8 (3.2)	2 (5.9)

Disposition	Palbociclib + ET (n = 136)	ET (n = 62)
Started tx, n (%)	135 (99.3)	60 (96.8)
▪ Receiving tx	24 (17.6)	8 (12.9)
▪ Discontinued tx	111 (81.6)	52 (85.5)
▪ PD	107 (78.7)	51 (82.3)
ITT, n*	136	62
Safety evaluable, n[†]	135	60

*All randomized patients.
[†]All patients who received ≥1 dose of study drug.

***Majority of patients received prior aromatase inhibition....

Llombart-Cussac. ASCO 2023. Abstr 1001.

PALMIRA: Investigator-Assessed PFS (Primary Endpoint)

	mPFS (Mo)	6-Mo PFS, %	12-Mo PFS, %
Palbociclib + ET	4.9	42.1	12.4
ET	3.6	29.1	12.3

Hazard ratio: 0.84 (95% CI: 0.66-1.07; 2-sided *P* = .149)
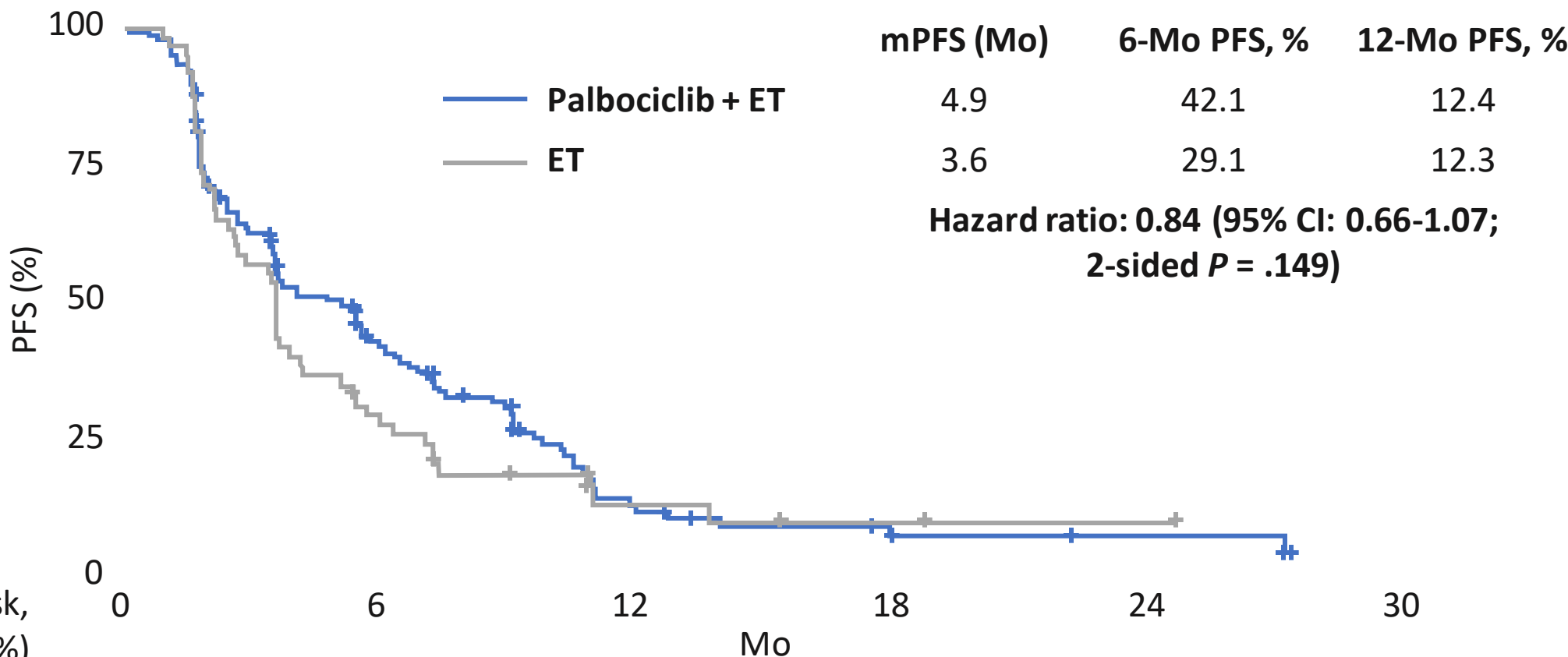
Patients at Risk, n (%)						
	0	6	12	18	24	30
Palbociclib + ET	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

PALMIRA: PFS Subgroup Analysis

	Palbociclib + ET (n = 136)		ET (n = 62)		Adjusted Hazard Ratio (95% CI)	Interaction P
	Events/n (%)	mPFS, Mo (95% CI)	Events/n (%)	mPFS, Mo (95% CI)		
All Patients	107/136 (78.7%)	4.9 (3.6-6)	51/62 (82.3%)	3.6 (2.5-4.2)	0.84 (0.66-1.07)	
Age						
<65 yr	73/94 (77.7%)	4.1 (3.5-5.8)	29/33 (87.9%)	2.7 (1.9-3.9)	0.71 (0.52-0.97)	0.239
≥65 yr	34/42 (81%)	5.5 (2.5-7.6)	11/29 (75.9%)	3.6 (3.5-7.1)	0.95 (0.75-1.4)	
Endocrine therapy						
Fulvestrant	96/120 (80%)	4.1 (3.5-5.8)	47/58 (81%)	3.6 (2.7-4.2)	0.86 (0.67-1.11)	0.313
Letrozole	11/16 (68.8%)	6.7 (2.5-14)	4/4 (100%)	3.1 (1.6-NA)	0.53 (0.21-1.30)	
ECOG performance status						
0	70/90 (77.8%)	4.9 (3.5-6.8)	25/31 (80.6%)	3.6 (1.9-7.3)	0.80 (0.58-1.11)	0.581
1 to 2	37/46 (80.4%)	4.1 (2.8-5.7)	26/31 (83.9%)	3.6 (2.5-5.5)	0.92 (0.64-1.32)	
Metastatic sites						
<3	65/92 (70.7%)	5.7 (3.6-7.4)	30/38 (78.9%)	3.7 (2.7-7.1)	0.91 (0.67-1.24)	0.374
≥ 3	42/44 (95.5%)	3.5 (2-5.5)	21/24 (87.5%)	2.9 (1.8-4.2)	0.73 (0.5-1.07)	
Visceral involvement						
No	34/52 (65.4%)	8.8 (4.2-11)	18/25 (72%)	4.4 (2.8-11.1)	0.94 (0.62-1.42)	0.239
Yes	73/84 (86.9%)	3.6 (2.3-5.4)	33/37 (89.2%)	2.8 (1.8-3.9)	0.79 (0.59-1.06)	
Duration of first-line palbociclib						
6-12 mo	14/18 (77.8%)	1.8 (1.7-12)	8/10 (80%)	3.5 (1-NA)	0.93 (0.5-1.73)	0.734
≥12 mo	93/118 (78.8%)	5.5 (3.6-6.4)	43/52 (82.7%)	3.6 (2.5-5.2)	0.83 (0.63-1.07)	

0.40 0.55 0.75 1.0 1.3 1.6 2.0

Palbociclib + ET Better   ET Better

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PALMIRA: Investigators' Conclusions

- In the phase II PALMIRA trial, 2L palbociclib maintenance + alternative ET vs alternative ET alone did not improve PFS in patients with HR+/HER2- ABC that progressed after clinical benefit on 1L palbociclib + ET
  - No significant improvements observed in any prespecified subgroup
  - Majority comparing palbo/fulvestrant to letrozole as > 88% received prior AI....
  - More "real world" comparison could have been against AI/mTOR or PI3K (or now elacestrant)
- Biomarker analysis ongoing to help identify patients most likely to benefit from CDK4/6 inhibitor maintenance in this setting
- At present, wouldn't recommend "palbociclib after palbociclib"

Llombart-Cussac. ASCO 2023. Abstr 1001.

Updates in Breast Cancer Brain Metastases:

HER2Climb
DESTINY-3
TUXEDO
DEBBRAH
TBCRC 022

Brain Metastases are a common consequence of advanced cancer

Primary site	Incidence Rates
Lung (overall)	16.3–19.9%
SCLC*	29.7% (at 5 years)
NSCLC*	12.6% (at 5 years)
Breast	10–15%
HER2 positive	25–50%
Triple negative	20% → 40 – 50%
Melanoma	6.9–7.4%
Renal	6.5–9.8%
Colorectal	3.0%

*can be up to 50–60% depending on study and disease duration

Glitza Oliva et al. Ann Oncol 2018;29: 1509–1520
Barnholtz-Sloan et al. J. Clin Oncol. 2004;22(14):2865–72
Schouten et al. Cancer. 2002;94(10):2698–705
Chamberalin et al. Neuro-Oncology. 2017;19(1):i1–i24

Multiple Presentations of Breast Cancer Brain Metastases

- Solitary lesion

Limited lesions

Multiple lesions

Fecci….Anders et al. CCR. 2019.
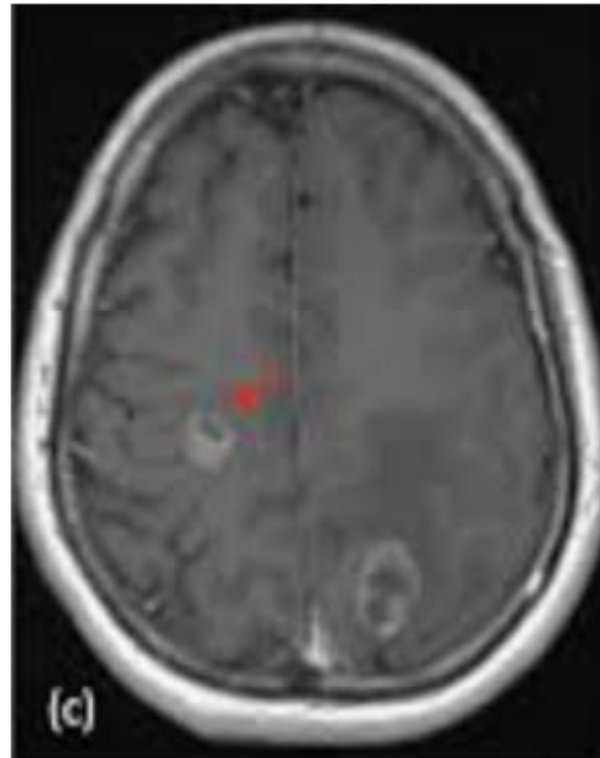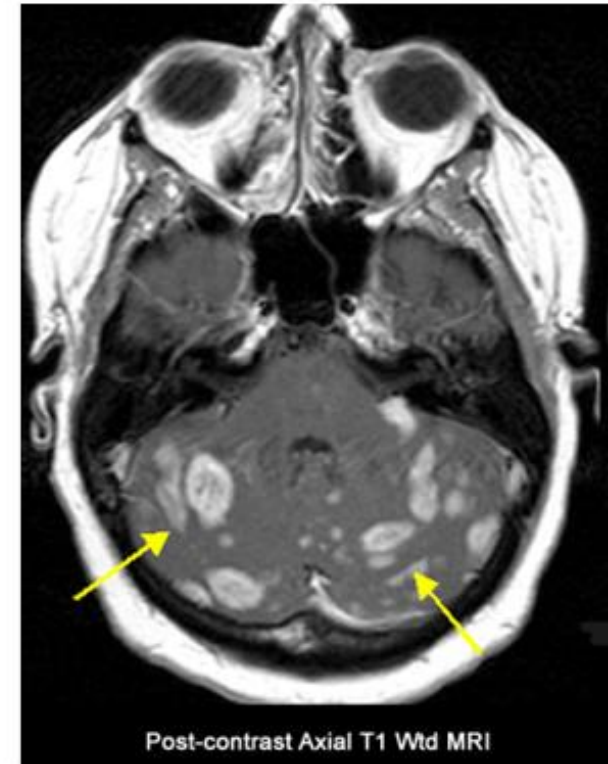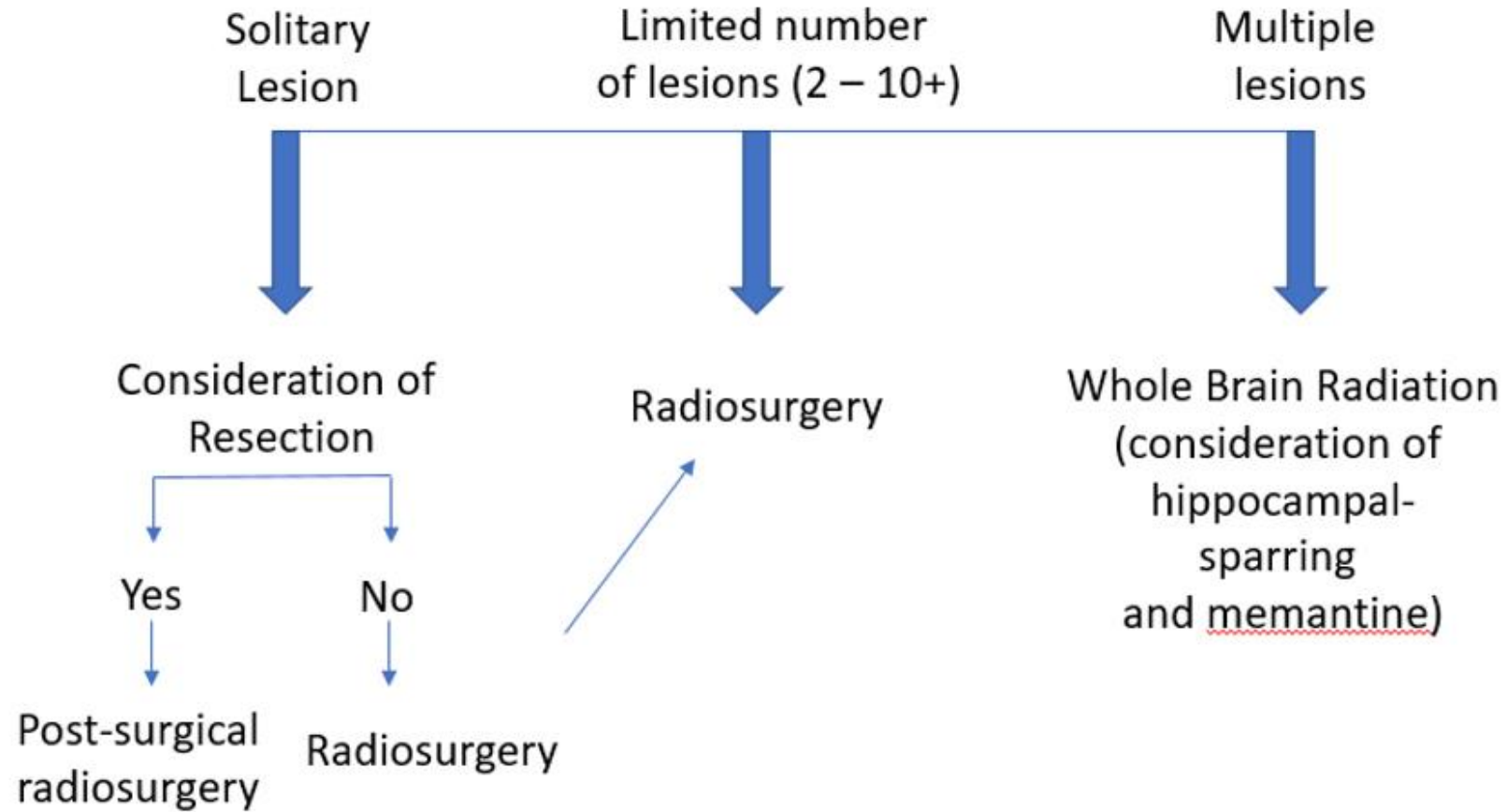
NCCN: Systemic Therapy Options expanded in 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY
BRAIN METASTASES[aa]

- Tumor Agnostic[bb]
  - *NTRK* gene fusion tumors
    - ◊ Larotrectinib[10]
    - ◊ Entrectinib[11]
  - TMZ 5/28 schedule

- Breast Cancer[cc]
  - HER2 positive
    - ◊ Ado-trastuzumab emtansine (T-DM1)[114]
    - ◊ Capecitabine + lapatinib[115,116]
    - ◊ Capecitabine + neratinib[117,118]
    - ◊ Paclitaxel + neratinib (category 2B)[119]
    - ◊ Tucatinib + trastuzumab[dd] + capecitabine (category 1)
      (if previously treated with 1 or more anti-HER2–based regimens)[120]
    - ◊ Fam-trastuzumab deruxtecan-nxki[121,122]
    - ◊ Pertuzumab and high-dose trastuzumab[dd,123]
  - HER2 non-specific
    - ◊ Capecitabine[124-128]
    - ◊ Cisplatin (category 2B)[129,130]
    - ◊ Etoposide (category 2B)[129,130]
    - ◊ Cisplatin + etoposide (category 2B)[130,131]
    - ◊ High-dose methotrexate (category 2B)[r,132]

- Melanoma[cc]
  - *BRAF* V600E positive
    - ◊ Dabrafenib[133-135]/trametinib[136]
    - ◊ Vemurafenib[137,138]/cobimetinib[ee] (category 2B)
  - *BRAF* non-specific
    - ◊ Ipilimumab + nivolumab (preferred)[139-141]
    - ◊ Ipilimumab[142]
    - ◊ Nivolumab[140]
    - ◊ Pembrolizumab[143]

- Non-Small Cell Lung Cancer[cc]
  - EGFR-sensitizing mutation positive
    - ◊ Osimertinib[144-146]
    - ◊ Pulsatile erlotinib[147-149]
    - ◊ Afatinib (category 2B)[150]
    - ◊ Gefitinib (category 2B)[151,152]
  - *MET* exon 14 mutated
    - ◊ Capmatinib[153]
  - *RET* fusion positive
    - ◊ Selpercatinib[154]
  - *ALK* rearrangement positive
    - ◊ Brigatinib[155,156]
    - ◊ Lorlatinib[157]
    - ◊ Alectinib[158,159]
    - ◊ Ceritinib[160]
  - *ALK* rearrangement positive or *ROS1* positive
    - ◊ Crizotinib (category 2B)[161]
  - PD-L1 positive
    - ◊ Pembrolizumab[143,162]
    - ◊ Nivolumab[163-165]

- Small Cell Lung Cancer[cc]
  - ◊ Topotecan (category 2B)

- Lymphoma[cc]
  - ◊ High-dose methotrexate[166]

Strategies with additional Data 2022-23:

HER2 TKIs:
Tucatinib
Neratinib
Pyrotinib

Her2 targeting ADC's:
TDM1
Trastuzumab Deruxtecan

MoAb::
High-dose trastuzumab/ pertuzumab

www.NCCN.org

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]

HER2CLIMB Randomized, Double-blind, Pivotal Trial

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

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

R* (2:1)

N=410

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

21-day cycle

N=202

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

21-day cycle

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

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 for patients receiving Tucatinib

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

A Overall survival

21.6 months (95% CI, 18.1-28.5 months)

12.5 months (95% CI, 11.2-16.9 months)

TUC+Tras+Cape

Pbo+Tras+Cape

No. at risk																	
TUC+Tras+Cape	198	183	166	147	131	118	105	92	68	54	36	22	14	9	8	6	2
Pbo+Tras+Cape	93	87	76	66	46	40	34	26	17	11	6	5	4	3	0	0	0

Lin N….Anders, CK…et. al. Jama Oncology, December 2022
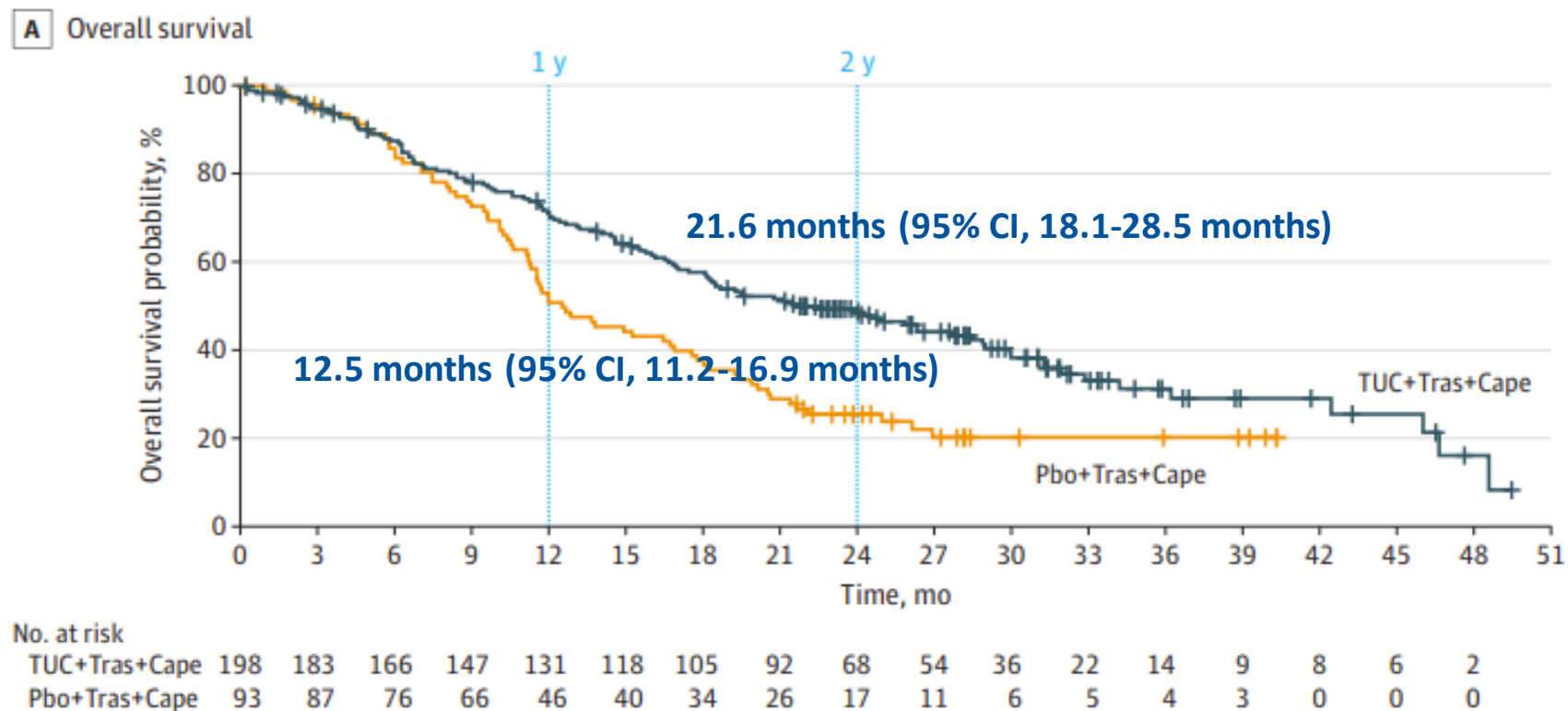
Improved intracranial PFS for patients receiving Tucatinib

B Intracranial progression-free survival
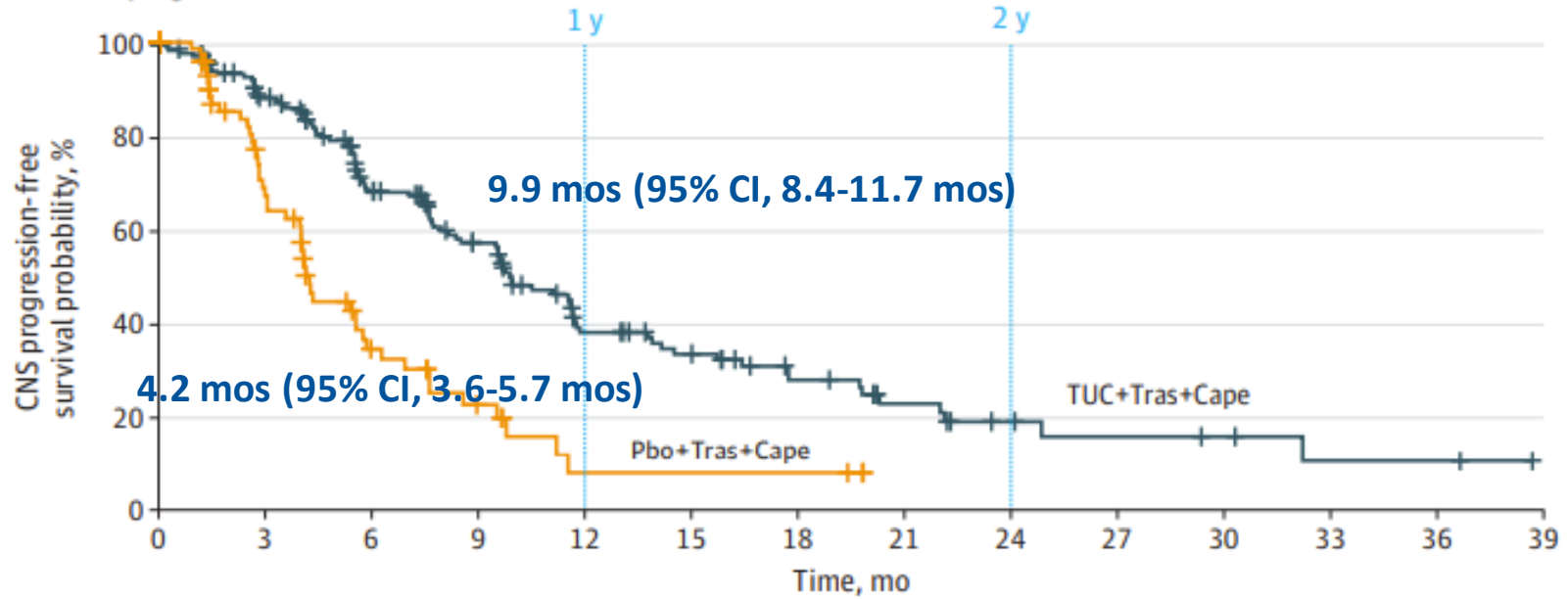
9.9 mos (95% CI, 8.4-11.7 mos)

4.2 mos (95% CI, 3.6-5.7 mos)

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

Improved time to New Brain Lesion for patients receiving Tucatinib

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

24.9 months (95% CI, 17.8-NR)

13.8 months (95% CI, 9.6 - NR)

Lin N….Anders, CK…et. al. Jama Oncology, December 2022
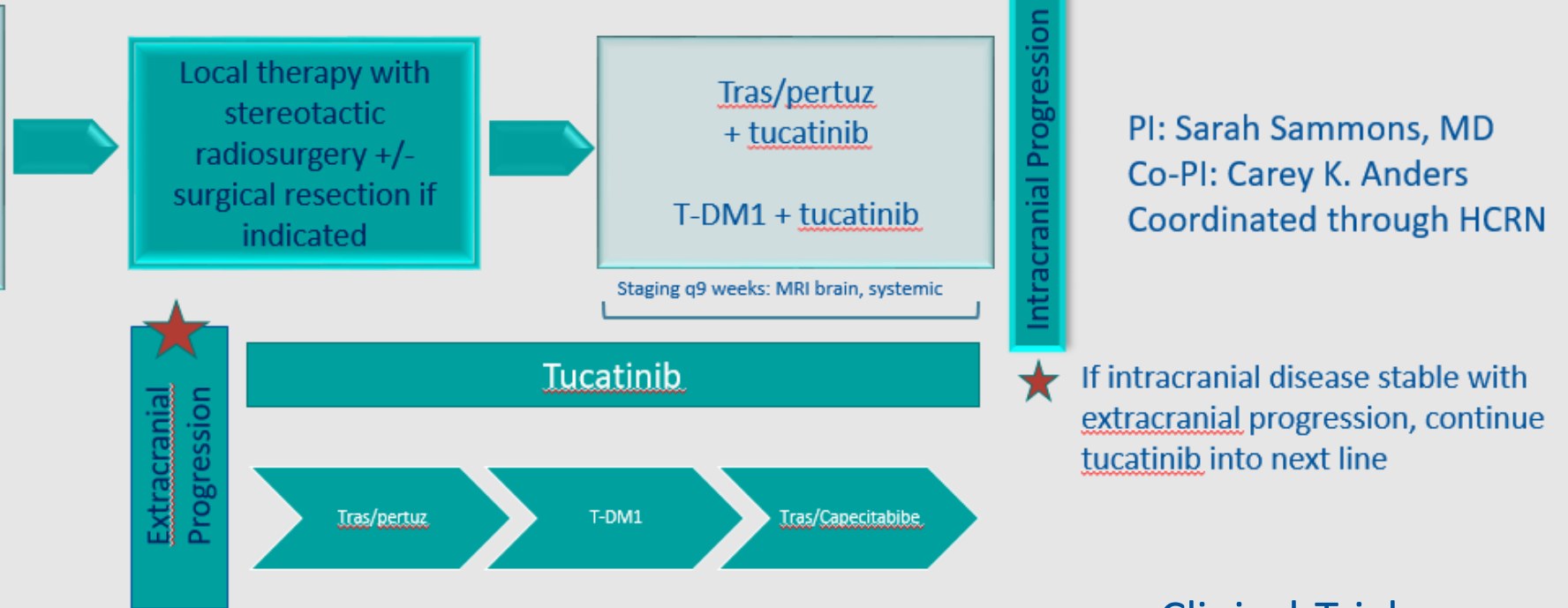
DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd
An open-label, multicenter study (NCT03529110)

Patients (N = 524)
- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]
- Could have clinically stable, treated brain metastases[c]
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

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

R 1:1

T-DXd 5.4 mg/kg Q3W (n = 261)[d]

T-DM1 3.6 mg/kg Q3W (n = 263)[e]
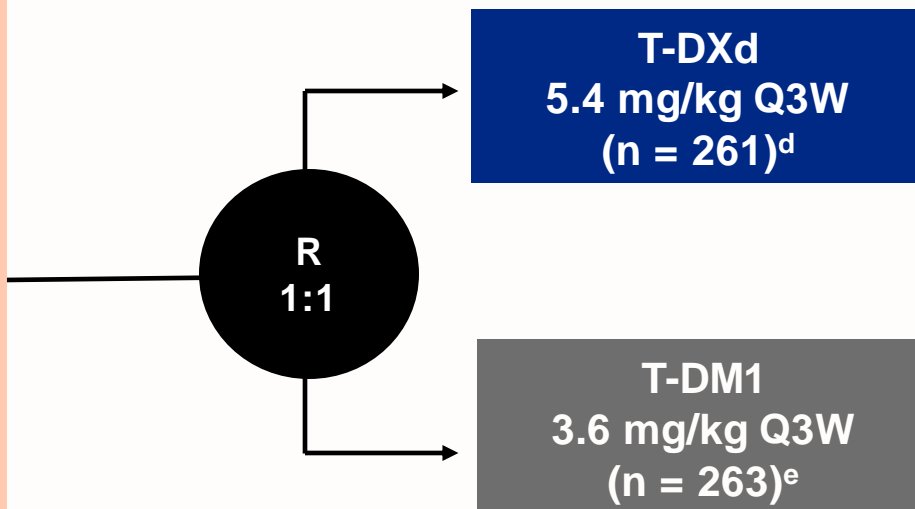
Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

20% in each arm with h/o Brain Mets

- At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment
- Median follow up was 15.9 months
- BMs were measured at baseline by CT or MRI and lesions were monitored throughout the study

BICR, blinded independent central review; BM, brain metastasis; CT, computed tomography; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imagining; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. [a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]Prior to protocol amendment, patients with stable, untreated BM were eligible. [d]4 patients were randomly assigned but not treated. [e]2 patients were randomly assigned but not treated.

Hurvitz et al. SABCS 2022.

Updated Primary Endpoint: PFS by BICR

mPFS was ~4X longer for T-DXd compared with T-DM1

T-DXd: 75.2% (95% CI, 69.3-80.2)
T-DM1: 33.9% (95% CI, 27.7-40.2)

T-DXd: 53.7% (95% CI, 46.8-60.1)
T-DM1: 26.4% (95% CI, 20.5-32.6)

Censor
T-DXd (n = 261)
T-DM1 (n = 263)

	T-DXd	T-DM1
Median (95% CI), months	28.8 (22.4-37.9)	6.8 (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	
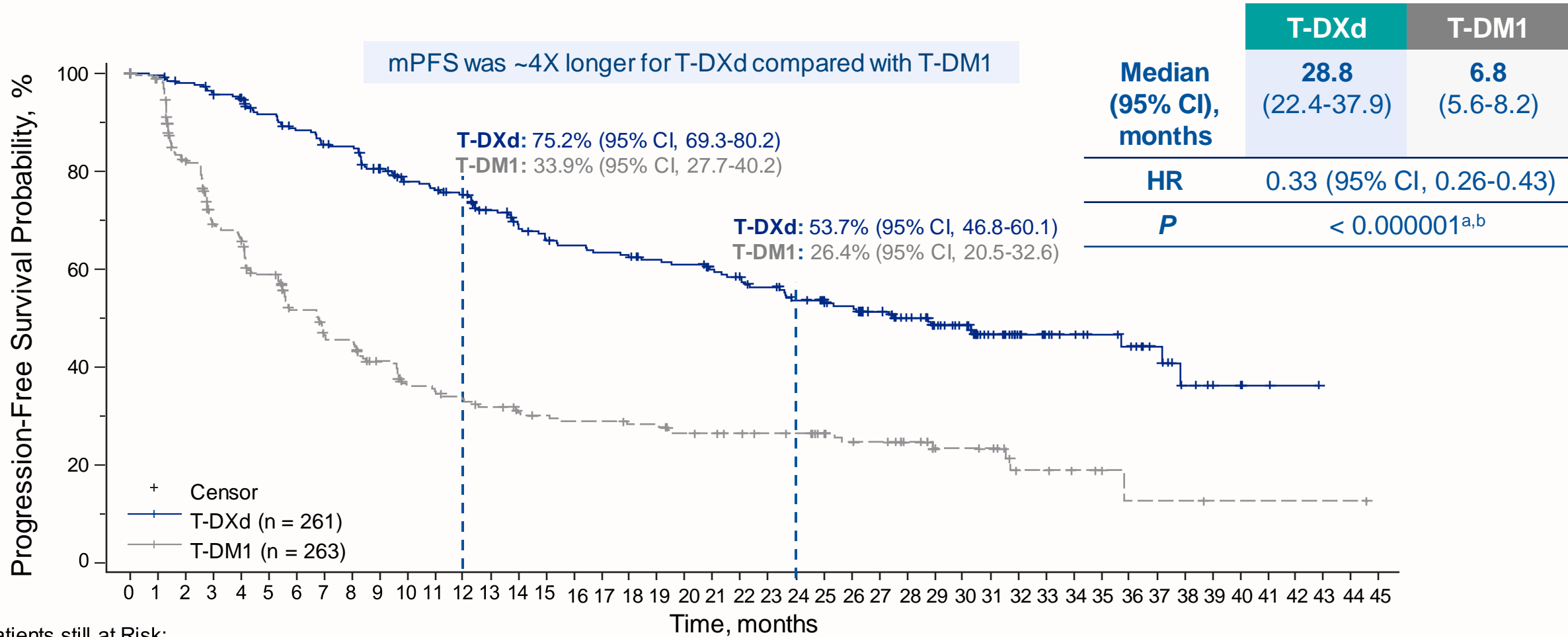
Patients still at Risk:

T-DXd   261 256 250 244 240 225 216 207 205 191 176 173 167 154 146 140 134 131 130 125 123 117 113 107 99 96 90 82 73 64 55 41 32 28 23 20 18 13 7 5 4 2 1 0

T-DM1   263 253 201 164 156 134 111 99 96 81 69 67 63 58 54 51 49 49 47 47 42 41 39 37 36 32 28 27 22 19 15 14 8 7 6 4 2 2 2 1 1 1 1 1 0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

Hurvitz et al. SABCS 2022.

PFS KM Curves for Patients With and Without BM

Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	0.25 (0.13-0.45)	
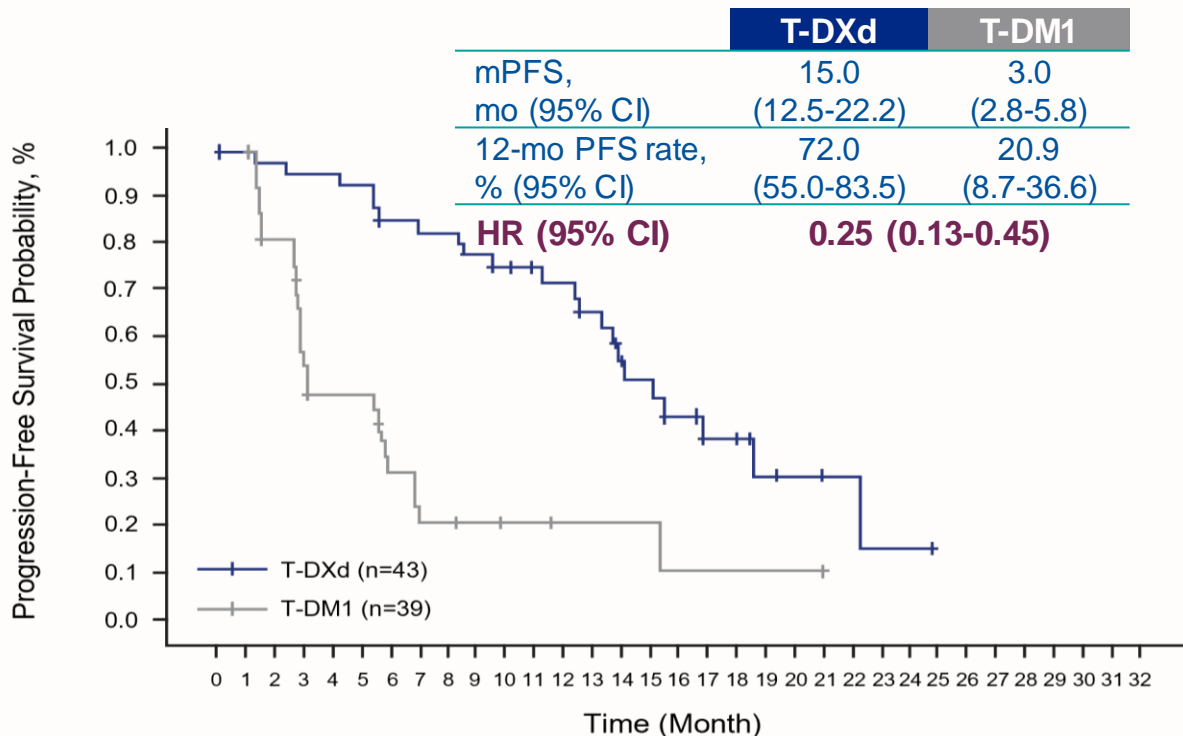
Patients Still at Risk:

T-DXd (43) 43 41 40 39 39 38 34 33 33 29 26 24 23 20 14 13 10 7 6 4 3 2 2 1 1 0 0 0 0 0 0 0 0
T-DM1 (39) 39 38 28 17 15 15 9 6 6 5 3 3 2 2 2 2 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0

At data cutoff, in patients with BM at baseline, PD was observed:
- In 21/43 treated with T-DXd versus 27/39 with T-DM1
  - In the brain in 9/21 treated with T-DXd versus 11/27 with T-DM1

No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	0.30 (0.22-0.40)	
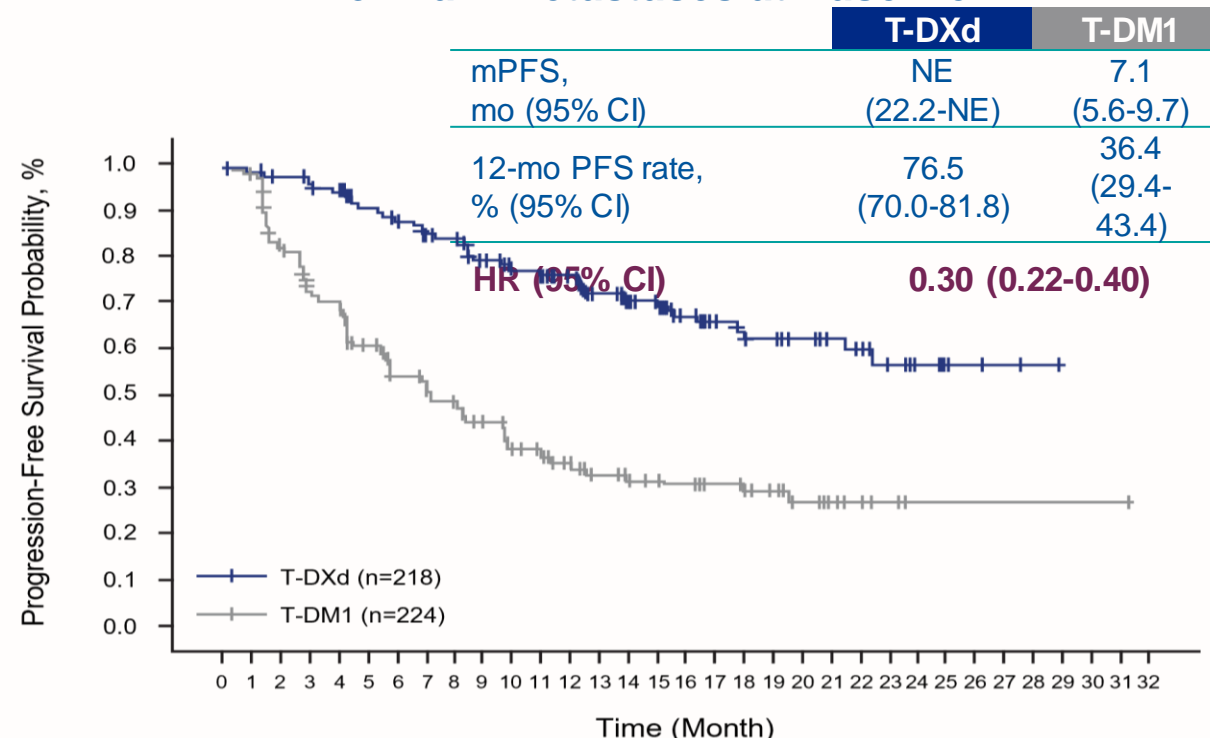
Patients Still at Risk:

T-DXd (218) 218 215 210 205 201 186 180 169 167 154 142 140 127 112 98 92 69 57 47 41 33 27 23 18 9 6 5 3 2 0 0 0 0
T-DM1 (224) 224 214 172 146 140 117 99 90 87 73 62 57 49 41 35 32 28 22 20 15 11 8 6 4 1 1 1 1 1 1 1 1 0

At data cutoff, in patients without BM at baseline, PD was observed:
- In 63/218 treated with T-DXd versus 128/224 with T-DM1
  - In the brain in 4/63 treated with T-DXd versus 1/128 with T-DM1

mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Hurvitz et al. SABCS 2021

Intracranial Response per BICR using RECIST 1.1

Best % Change in Sum of Diameters from Baseline

T-DXd (n = 21)

T-DM1 (n = 23)
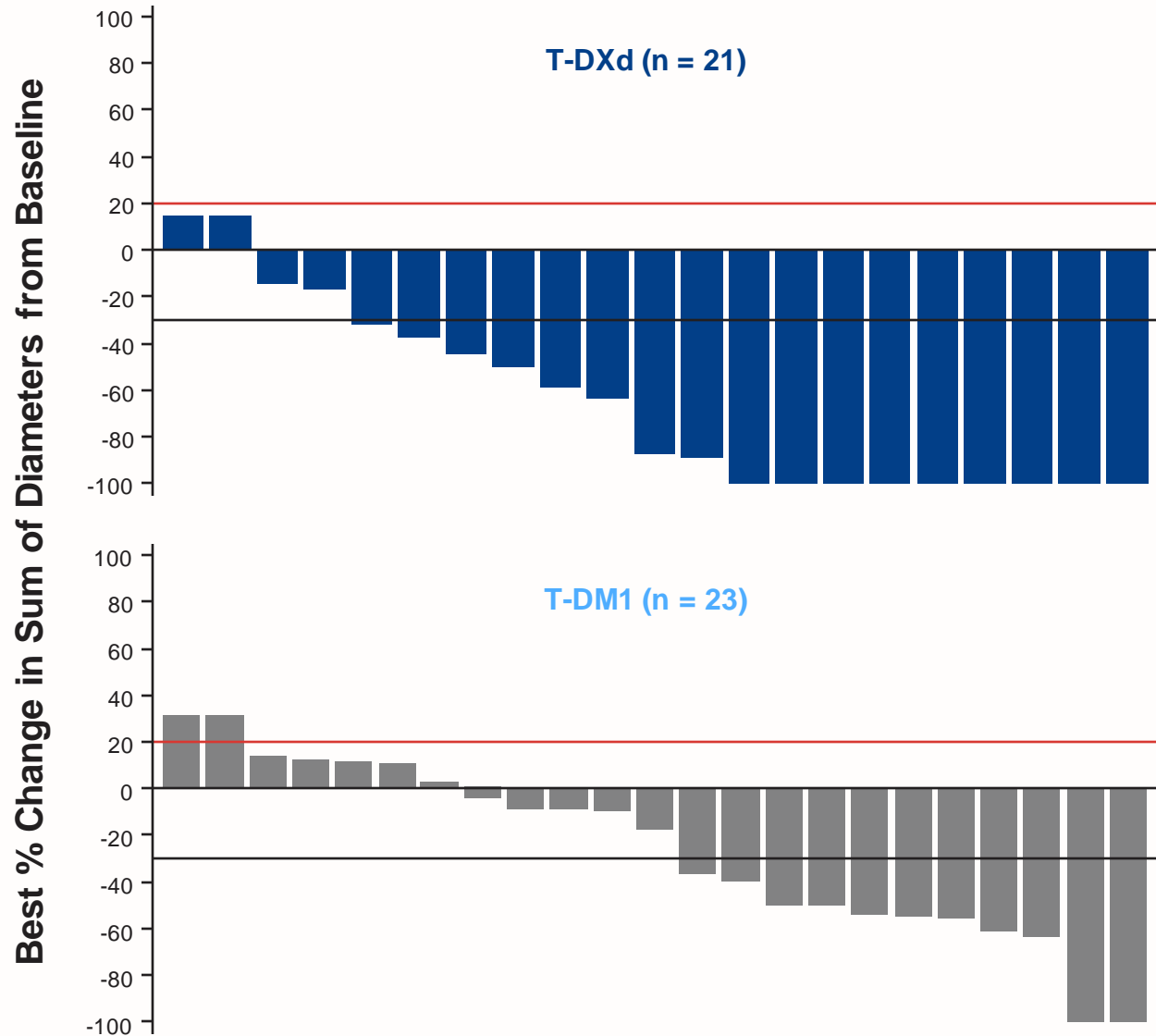
	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Hurvitz et al. SABCS 2021

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

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],

Median PFS = 14 mos
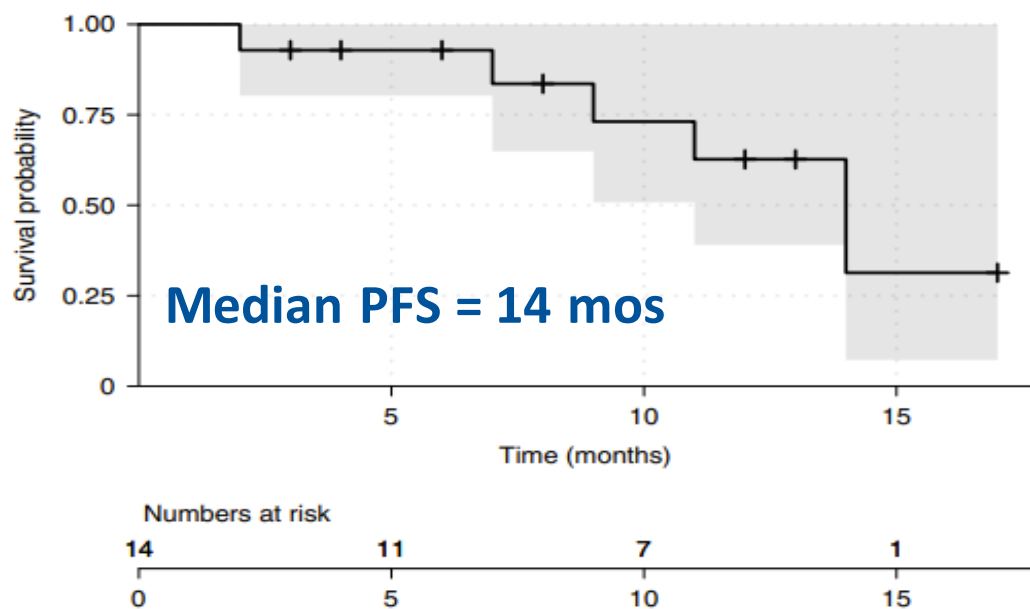
Fig. 3 | Kaplan–Meier plot showing progression-free survival times (months) in the TUXEDO-1 trial.
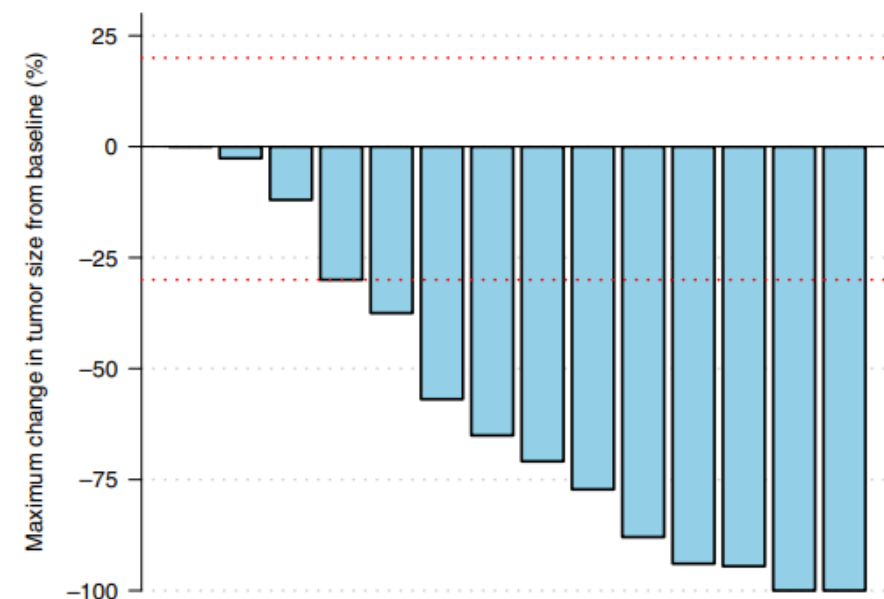
Fig. 2 | Waterfall plot of responses in patients evaluable for response by RANO-BM criteria in the TUXEDO-1 trial. Blue bars illustrate the radiographic change of maximum brain metastasis size after start of trastuzumab deruxtecan therapy compared to the baseline measurement. Red dotted lines denote thresholds for response and progression by RANO-BM criteria.

Bartsch et al. Nat Medicine, 2022

TDxd in Her2+ *Active* Breast Cancer Brain Metastases

DF-BM 1409 ER+ HER2-low (IHC 2+, FISH negative)
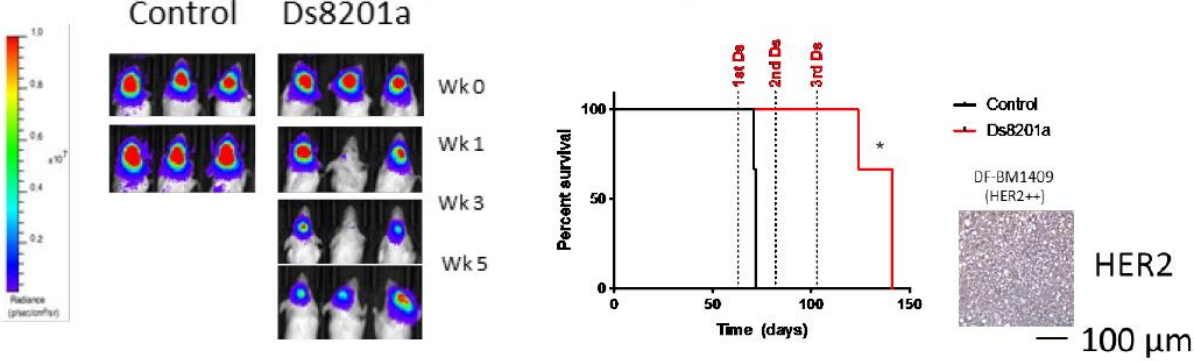
DF-BM355TDM1-resistant model (HER2 3+)
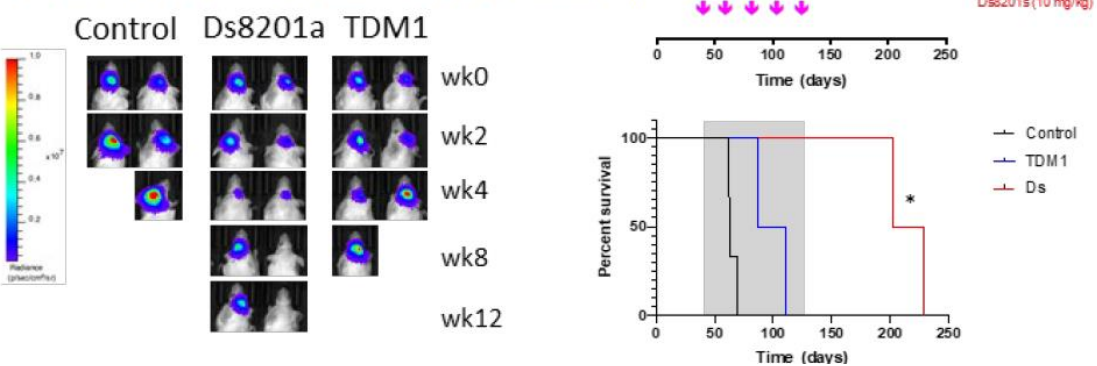
Additional modeling illustrates efficacy of TDxD in Her2+brain Metastases murine (PDX) models – both ER+ and ER -
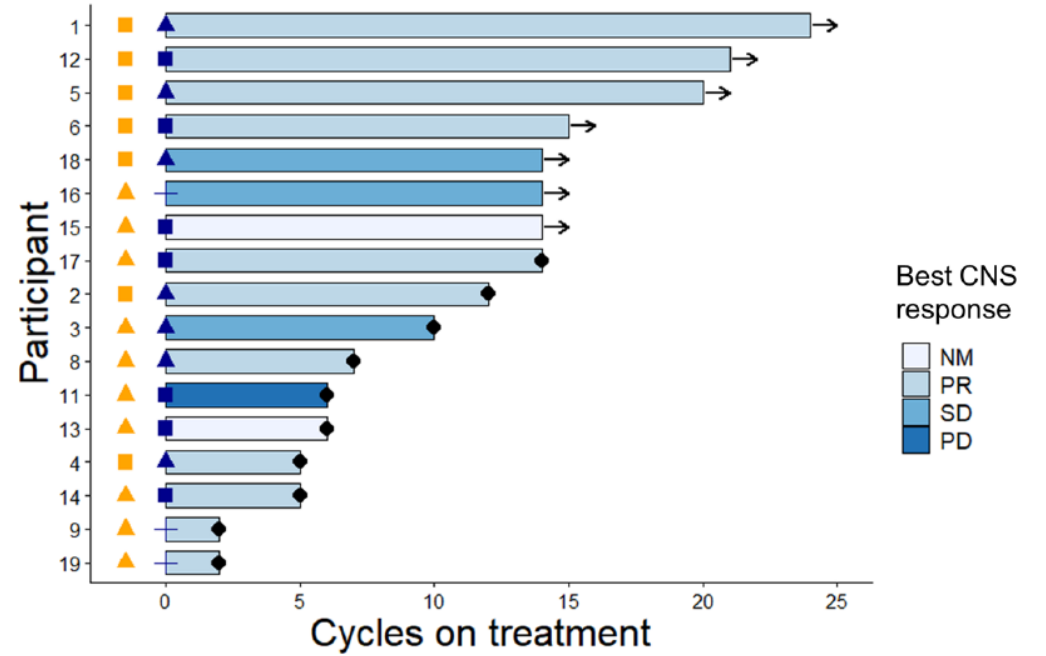
17 participants with active brain mets (median 14 mos since radiation therapy): iORR 73% (11/15 with measureable dz

Kabraji et al. CCR. 2022.

Key Eligibility Criteria

➡ Female or male pts aged ≥18 years

➡ HER2^{+} or HER-LE ABC with stable, progressing, or untreated BMs and/or LMC

➡ ECOG PS 0 or 1 (0–2 for **cohort 5**)

➡ Pts with HER2^{+} ABC: Prior treatment with a taxane and ≥1 line of anti-HER2 therapy in the metastatic setting

➡ Pts with HER2-LE ABC and:

- HR[-]: ≥1 prior regimen of CT in the metastatic setting
- HR[+]: 1 prior line of ET and ≥1 prior regimen of CT in the metastatic setting

➡ **Cohorts 2, 3, 4:** Measurable brain disease by on T1-weighted, gadolinium-enhanced MRI
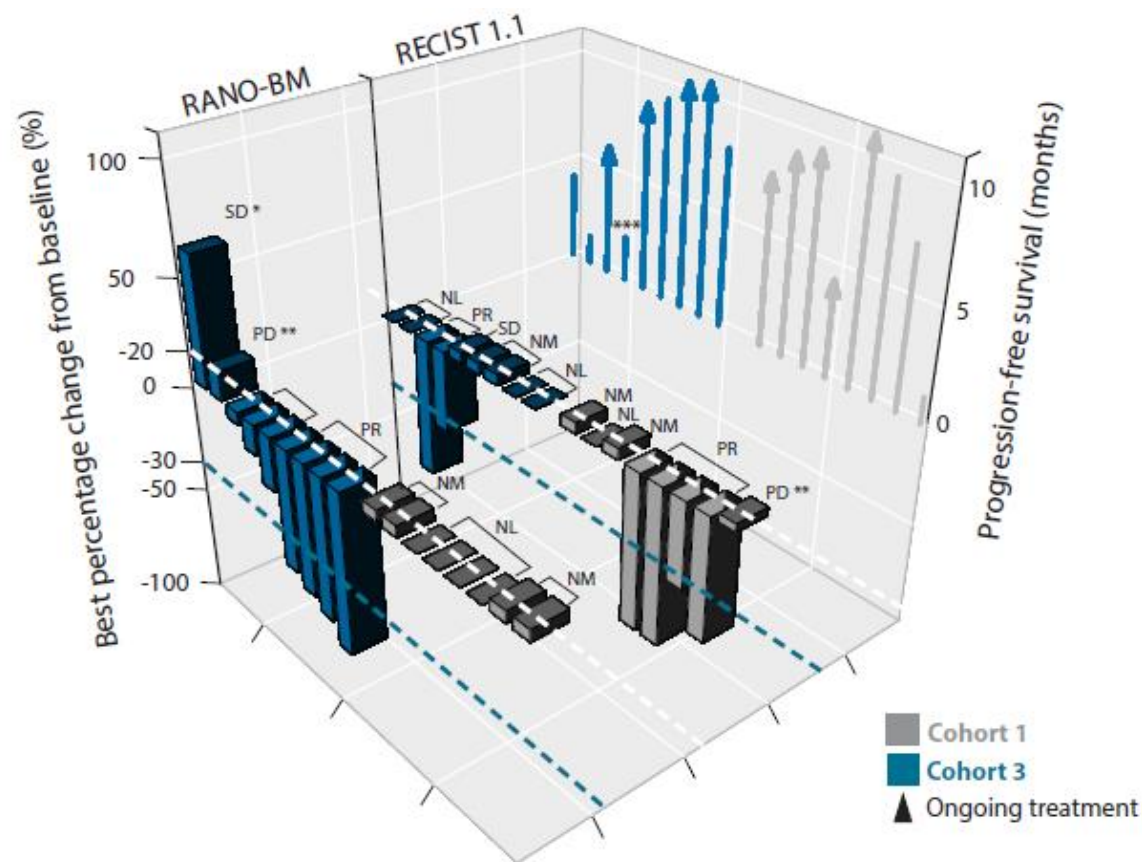
➡ **Cohort 5:** LMC with CSF[+] cytology

Cohort 1: HER2^{+} ABC with stable BMs after surgery, SRS and/or WBRT — N=8

Cohort 2: HER2^{+} or HER2-LE ABC with asymptomatic untreated BMs — N=10

Cohort 3: HER2^{+} ABC with progressing BMs after surgery, SRS and/or WBRT — N=9

Cohort 4: HER2-LE ABC with progressing BMs after surgery, SRS and/or WBRT — N=7

Cohort 5: HER2^{+} or HER2-LE ABC with LMC — N=7

T-Dxd 5.4 mg/kg IV Q3W

Efficacy In Cohort 1

- 7 of 8 pts (87.5.%) with stable BMs at baseline were alive without PD at 16 weeks, reaching the primary endpoint ($P < 0.001$).

Table 2. Best Overall Intracranial Response (RANO-BM) In Cohort 3

Response	Cohort 3 (n=9)
Best overall intracranial response, n (%)	
CR	0 (0)
PR	4 (44.4)
SD ≥ 24 weeks	1 (11.1)
SD < 24 weeks	3 (33.3)
PD	1 (11.1)
ORR-IC, % (95% CI)	44.4 (13.7–78.8)
CBR-IC, % (95% CI)	55.6 (21.2–86.3)

Abbreviations: 95% CI, 95% of confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Batista et al. SABCS 2021.

José Manuel Pérez-García[1,2], Marta Vaz Batista[2,3], Patricia Cortez[4], Manuel Ruiz-Borrego[5], Juan Miguel Cejalvo[6], Juan de la Haba-Rodriguez[7], Laia Garrigós[1,8], Fabricio Racca[9], Sonia Servitja[10], Salvador Blanch[2,11], María Gion[12], Monica Nave[14], María Fernández-Abad[12,13], Alejandro Martinez-Bueno[8], Antonio Llombart-Cussac[2,15,16], Miguel Sampayo-Cordero[2], Andrea Malfettone[2], Javier Cortés[1,2,17]*, Sofía Braga[3]*

Background
- Destiny-04: T-DXd significantly improved survival in Her2-low ABC
- Anti-tumor activity of T-DXd observed in Her2+ BCBM
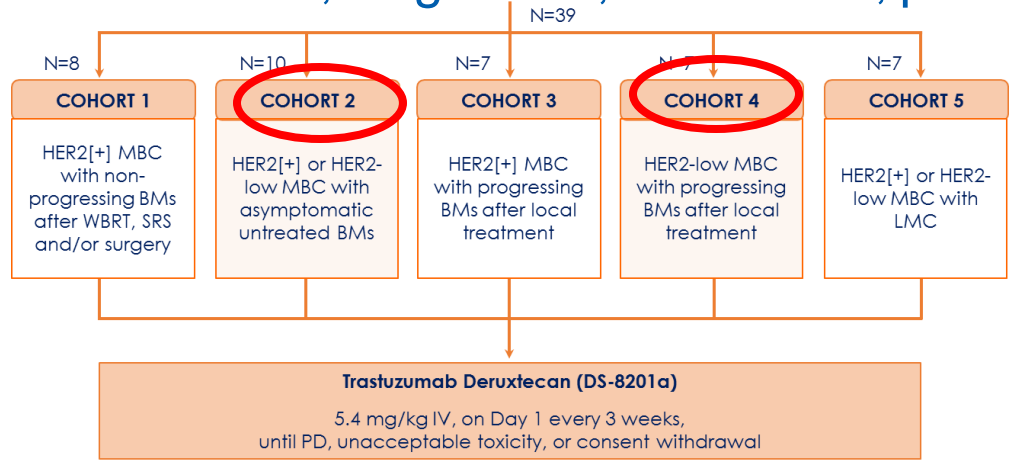→ Little known about T-DXd in Her2-low BCBM

Purpose
Evaluate efficacy and safety of **HER2-low** ABC pts in **cohorts 2/4**

STUDY DESIGN

Investigator-initiated multicenter, single-arm, five-cohort, phase 2 trial

| Baseline characteristics, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
Age, median (range), years	50 (40-72)	62 (48-73)	54 (40-73)
Female, %	100%	100%	100%
ECOG PS, %			
0	5 (83.3%)	1 (16.7%)	6 (50%)
1	1 (16.7%)	5 (83.3%)	6 (50%)
Measurable systemic disease at baseline			
Intracranial	6 (100%)	6 (100%)	12 (100%)
Extracranial	5 (83.3%)	6 (100%)	11 (91.7%)
Number of metastatic organ sites			
1	0 (0%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	0 (0%)
≥ 3	6 (100%)	6 (100%)	12 (100%)
HER2 status (IHC, %)			
1+	5 (83.3%)	5 (83.3%)	10 (83.3%)
2+/ISH non-amplified	1 (16.7%)	1 (16.7%)	2 (16.7%)
Histology, %			
ER+ and/or PgR+	5 (83.3%)	4 (66.7%)	9 (75%)
ER- and PgR-	1 (16.7%)	2 (33.3%)	3 (25%)
Any prior therapy for BMs, %			
WBRT	0 (0%)	5 (83.3%)	5 (41.7%)
SRS/SRT	0 (0%)	3 (50%)	3 (25%)
Surgery	0 (0%)	1 (16.7%)	1 (8.3%)
Number of previous lines in advance disease Median (Min; Max)	7 (4; 8)	3 (2; 4)	4 (2; 8)
Duration in months of last prior therapy Median (Min; Max)	4,6 (0,7; 12,6)	3,3 (1,4; 11,2)	4,2 (0,7;12,6)
Previous systemic cancer therapy, %			
Anti-HER2 (Trastuzumab)*	0 (0%)	1 (16.7%)	1 (8.3%)
Chemotherapy	6 (100%)	6 (100%)	12 (100%)
Endocrine therapy	5 (83.3%)	4 (66.7%)	9 (75%)

- Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; IHC, immunohistochemistry; ISH, *in situ* hybridization; PgR, progesterone receptor; SRS/SRT, stereotactic radiosurgery/stereotactic radiotherapy; WBRT, whole brain radiation therapy.
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population
- * This patient started DEBBRAH study as IHC 2+/ISH negative. She received 3 previous lines of therapy for advanced disease, including trastuzumab.

Table 2. Best Intracranial Response (RANO-BM) in HER2-Low Patients

Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
Overall Response, n (%)			
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	4 (66.7%)	2 (33.3%)	6 (50.0%)
SD ≥ 24w	1 (16.7%)	1 (16.7%)	2 (16.7%)
SD < 24w	1 (16.7%)	3 (50.0%)	4 (33.3%)
PD	0 (0.0%)	0 (0.0%)	0 (0.0%)
ORR-IC, n (%)	4 (66.7%)	2 (33.3%)	6 (50.0%)
CBR-IC, n (%)	5 (83.3%)	3 (50.0%)	8 (66.7%)
DoR-IC, Median (Min; Max)	3.6 (2.0; 7.1)	7.8 (7.3; 8.3)	5.8 (2.0; 8.3)
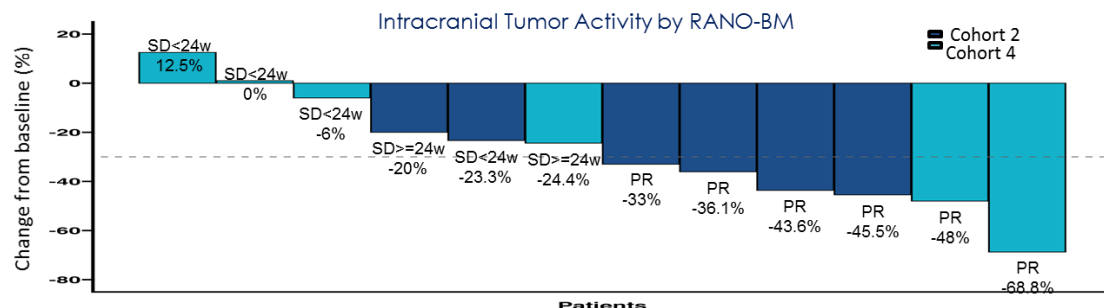
Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
ORR, n (%)	3 (50.0%)	2 (33.3%)	5 (41.7%)
CBR, n (%)	3 (50.0%)	3 (50.0%)	6 (50.0%)
DoR, Median (Min; Max)	4.5 (3.5; 7.1)	5.8 (5.5; 6.1)	5.5 (3.5; 7.1)
PFS		5.67 months (95% CI:4.7-NA) (Events: 9/12)	

- Abbreviations: 95% CI, 95% of confidence interval; NA, not achieved
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population

System Organ Class Preferred term, n (%)	Overall (n=12)	
	Any grade	**Grade 3**
ANY	**10 (83.3%)**	**2 (16.7%)**
HEMATOLOGICAL	**3 (25.0%)**	**1 (8.3%)**
Anemia	2 (16.7%)	0 (0%)
Neutropenia	2 (16.7%)	0 (0%)
NON-HEMATOLOGICAL	**10 (83.3%)**	**1 (8.3%)**
Fatigue	7 (58.3%)	1 (8.3%)
Nausea	6 (50.0%)	0 (0%)
Vomiting	4 (33.3%)	0 (0%)
Gamma-glutamyltransferase increased	2 (16.7%)	0 (0%)
Interstitial lung disease/pneumonitis	2 (16.7%)	0 (0%)
Diarrhea	2 (16.7%)	0 (0%)

At data cutoff, 12 patients who were enrolled in the two cohorts, received at least one dose of study drug and were included in the safety set.

Intracranial Tumor Activity by RANO-BM

Perez-Garcia, JM et al SABCS, 2022

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

Rachel A Freedman[1], Siyang Ren[1], Nabihah Tayob[1], Rebecca S. Gelman[1], Karen L. Smith[2], Raechel Davis[1], Alyssa Pereslete[1], Victoria Attaya[1], Christine Cotter[1], Wendy Y. Chen[1], Cesar A. Santa-Maria[2], Catherine Van Poznak[3], Beverly Moy[4], Adam M. Brufsky[5], Michelle E. Melisko[6], Ciara C. O'Sullivan[7], Nadia Ashai[8], Yasmeen Rauf[9], Julie R. Nangia[10], Dario Trapani[1], Robyn T. Burns[11], Jennifer Savoie[1,11], Antonio C. Wolff[2], Eric P. Winer[12], Mothaffar F. Rimawi[10], Ian E. Krop[12], Nancy U Lin[1] on behalf of the TBCRC

Background

Neratinib may overcome T-DM1 resistance, and the combination has potential CNS efficacy.

Purpose

Report results of neratinib plus T-DM1 in HER2+ BCBM
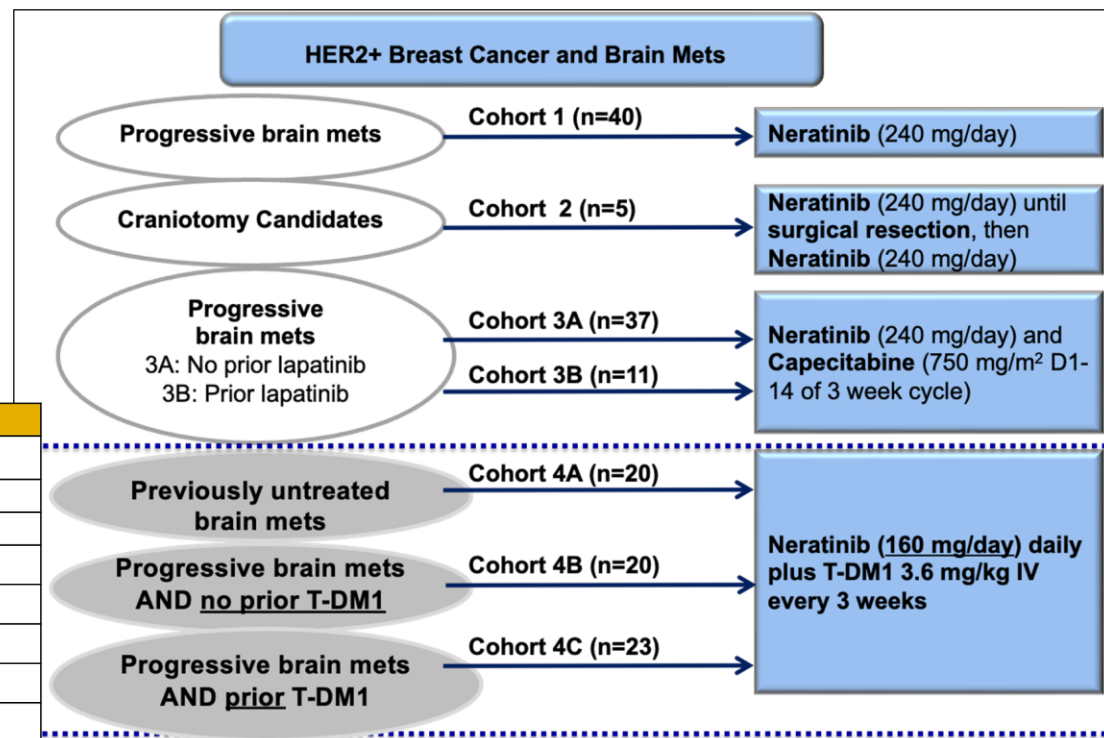
Characteristic	Cohort 4A (n=6)	Cohort 4B (n=17)	Cohort 4C (n=21)
Age (median, range)	52 (44-65)	48 (42-59)	48 (35-68)
Non-white race	2 (33.0)	3 (17.6)	1 (4.8)
# of prior chemo lines for MBC		Median = 2 (range 0-10)	
1	1 (16.7)	9 (52.9)	0 (0)
2	1 (16.7)	4 (23.5)	6 (28.6)
3+	1 (16.7)	3 (17.6)	15 (71.4)
Missing	3 (50)	1 (5.9)	0 (0)
Prior tucatinib	0 (0)	0 (0)	0 (0)
Prior CNS surgery	0 (0)	7 (41.2)	7 (33.3)
Prior WBRT	0 (0)	12 (70.6)	11 (52.4)
Prior SRS	1 (16.7)	12 (70.6)	10 (47.6)

HER2+ Breast Cancer and Brain Mets

Progressive brain mets — Cohort 1 (n=40) → Neratinib (240 mg/day)

Craniotomy Candidates — Cohort 2 (n=5) → Neratinib (240 mg/day) until surgical resection, then Neratinib (240 mg/day)

Progressive brain mets
3A: No prior lapatinib
3B: Prior lapatinib
— Cohort 3A (n=37), Cohort 3B (n=11) → Neratinib (240 mg/day) and Capecitabine (750 mg/m² D1-14 of 3 week cycle)

Previously untreated brain mets — Cohort 4A (n=20)

Progressive brain mets AND no prior T-DM1 — Cohort 4B (n=20)

Progressive brain mets AND prior T-DM1 — Cohort 4C (n=23)

→ Neratinib (160 mg/day) daily plus T-DM1 3.6 mg/kg IV every 3 weeks

Prospective, multicenter, phase 2
- Diarrhea ppx for Cycle 1
- Terminated early due to slow accrual

Figure 2. Waterfall Plot- % CNS Response
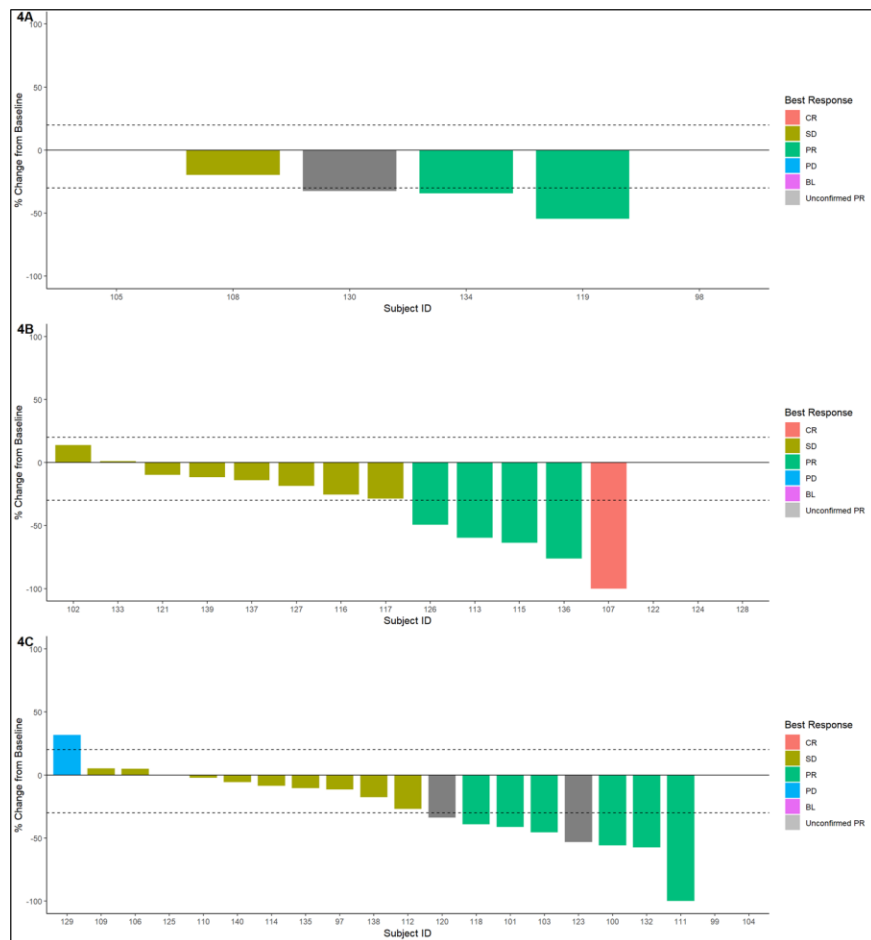
4A: Untreated   4B: No prior TDM1   4C: Prior TDM1

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%)

Freedman RA et al SABCS, 2022

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