ASCO and ESMO Updates 2023 Metastatic Breast Cancer

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Key Druggable Pathways and/or Targets in MBC

	Objective Response	Progression-Free Survival	Overall Survival	Agents with OS Benefit	Other Agents
PATHWAY – pathway signaling disruption mediates anti-tumor effects					
✓ ER-mediated signaling	X	X	X	Tamoxifen Aromatase inhibitors	Elacestrant
✓ CDK4/6-mediated signaling	X	X	X	Ribociclib Abemaciclib	Palbociclib
✓ PI3K/AKT/mTOR signaling	X	X			Alpelisib Everolimus Capivasertib
✓ Immune checkpoints	X	X	X	Pembrolizumab	
✓ DNA repair	X	X			Olaparib Talazoparib
✓ Few/rare alterations ✓ NTRK fusions (secretory) ✓ HER2 (lobular) ✓ dMMR/MSI-H	 X X X	 X X X			 Entrectinib Neratinib Pembrolizumab
TARGET - for anti-drug conjugates & delivery of toxic payloads					
✓ HER2	X	X	X	Trastuzumab deruxtecan	
✓ TROP2	X	X	X	Sacitizumab govitecan Datopotumab	

CDK4/6 Inhibitors as First-line Therapy

	PALOMA-2[1,2] First line N= 666	MONALEESA-2[3,4, 13] First line N=668	MONARCH-2[15,16] First and Second line N= 669	MONARCH-3[5.6] First line N= 493	MONALEESA-3[†7-9,14] First and Second line N= 726	MONALEESA-7*[10-13] First line N=672
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Abemaciclib	Ribociclib	Ribociclib
Endocrine partner	Letrozole	Letrozole	Fulvestrant	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
Patient population	Postmeno	Postmeno	Pre/postmeno	Postmeno	Postmeno	Pre/perimeno
mOS, mo	53.9 vs 51.2	63.9 vs 51.4	46.7 vs 37.3	67.1 vs 54.5	67.6 vs 51.8	58.7 vs 48
▪ HR	0.956	0.76; p = .008	0.757; p = 0.01	0.75; p=0.03 NS	0. 67; P = .00455	0.763; P = .00973
mPFS, mo	27.6 vs 14.5	25.3 vs 16.0	16.4 vs 9.3	28.18 vs 14.76	33.6 vs 19.2	23.8 vs 13.0
▪ HR	0.563	0.568	0.55	0.54	0.55[‡]	0.55
ORR, %	55.3 vs 44.4	52.7 vs 37.1	48 vs 21	59 vs 44	40.9 vs 28.7[†]	41 vs 30

*First-line ET; up to 1 previous CT line permitted in advanced setting (14% had received CT). [†]Includes first and second line. [‡]Descriptive analysis.

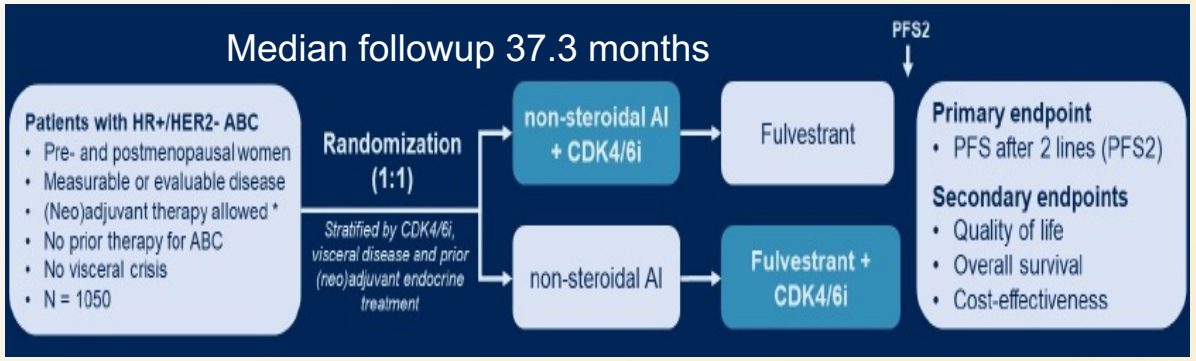
Factors influencing selection of CDK4/6i

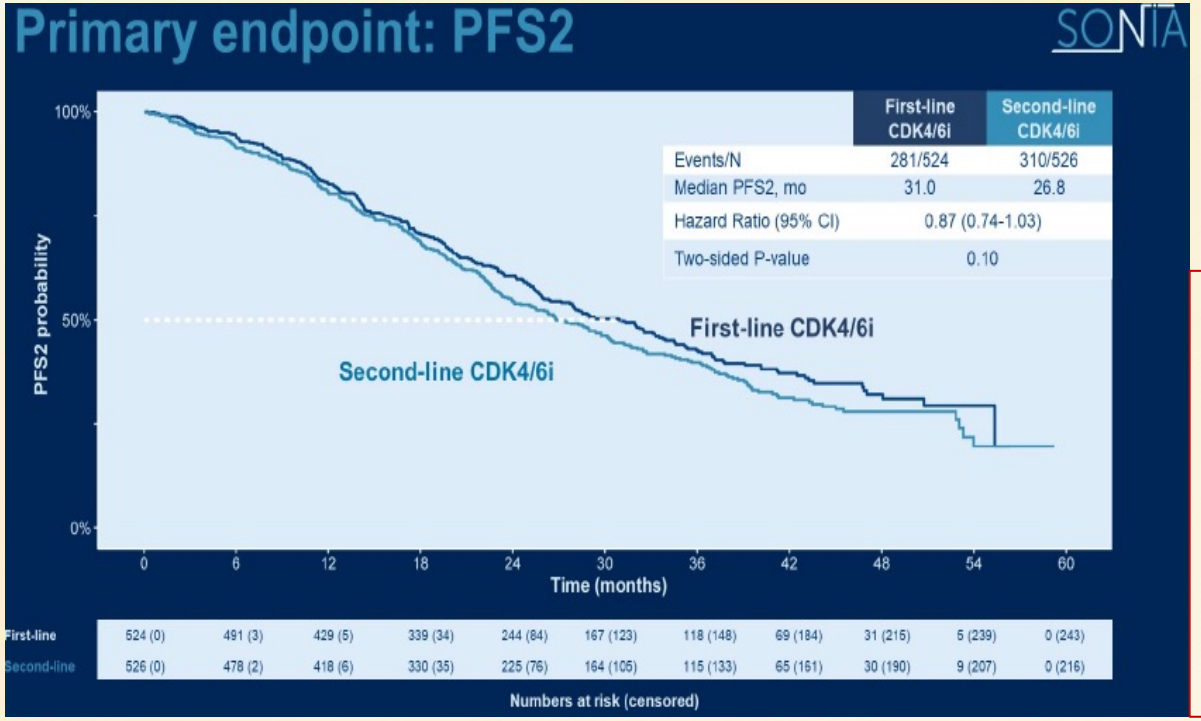
- Menopausal status
- Toxicity Profile
- Overall survival
- Co-morbidities: EKG, GI

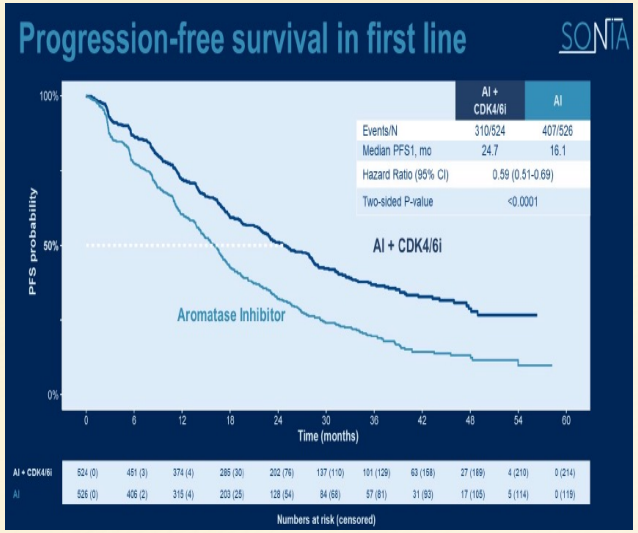
1. Finn. NEJM. 2016;375:1925.
2. Rugo. Breast Cancer Res Treat. 2019;174:719.
3. Hortobagyi. NEJM. 2016;375:1738.
4. Hortobagyi. Ann Oncol. 2018;29:1541.
5. Goetz. JCO. 2017;35:3638.
6. Johnston. NPJ Breast Cancer. 2019;5:5.
7. Slamon. JCO. 2018;36:2465.
8. Slamon. NEJM. 2020;382:514.
9. Slamon. ESMO 2019. Abstr LBA7_PR.
10. Tripathy. Lancet Oncol. 2018;19:904.
11. Hurvitz. ASCO 2019. Abstr LBA1008.
12. Im. NEJM. 2019;381:307.
13. Lu CCR 2022;28:851
14. Neven. ESMO Breast 2022
15. Sledge GW JCO 2017;35;2875
16. Sledge GW JAMAOncol 2020; 6:116

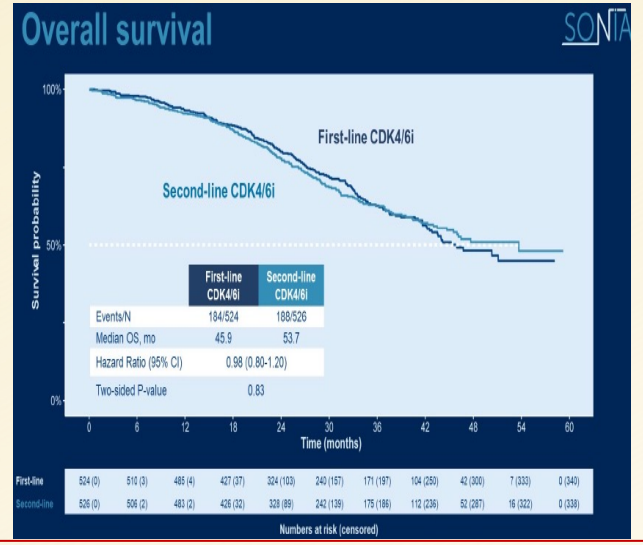
SONIA: Palbociclib for First or Second-Line ET:

Evidence favoring use of palbociclib for with 2nd-line rather than 1st-line









- **Comparison of 1st vs. 2nd-line palbociclib**
  - Primary endpoint – PFS2
    - Median 31.0 vs. 26.8 mo. (HR 0.87, 95% CI [0.74, 1.03]; P = .10)
  - Secondary endpoint – Overall Survival
    - Median 45.9 vs. 53.7 mo. (HR 0.98, 95% CI [0.80, 1.20]; P = .83).
  - Other findings:
    - Longer duration of palbociclib: 24.6 vs. 8.1 months
    - $200K higher drug expenditure
    - 1.7-fold more >/= grade 3 adverse events
    - Improved PFS1 - Median 24.7 vs. 16.1 (HR 0.59, [95% CI 0.51-0.69, p<0.0001)

Sonke et al. ASCO 2023 (DOI: 10.1200/JCO.2023.41.17_suppl.LBA1000)

RIGHT Choice (Phase 2, subgroup analysis): 1L ribociclib + endocrine therapy vs chemo among HR+/HER2– advanced breast cancer ± visceral crisis

- **Lu Y-S, et al. SABCS 2022:** RIGHT Choice reported significant median PFS benefit of ~1 year with ribociclib + ET vs combo CT 24.0 vs 12.3 months; HR 0.54 (95% CI 0.36–0.79)
- Exploratory subgroup analysis: Key efficacy endpoints from RIGHT Choice in patients ± visceral crisis; final database lock (cut-off 10 May 2023) PFS was 21.8 vs 12.8 months; HR 0.61 (95% CI 0.43-0.87; P=0.003)

Key eligibility

- Pre- and perimenopausal women
- HR+/HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease
- Aggressive disease
- ECOG PS ≤2
- Total bilirubin ≤1.5 x ULN

R
1:1

N=222

Ribociclib + ET
(600 mg, 3 weeks on/
1 week off)
+
Letrozole or anastrozole + goserelin

Combination CT
Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Primary endpoint:

- PFS

Secondary endpoints:

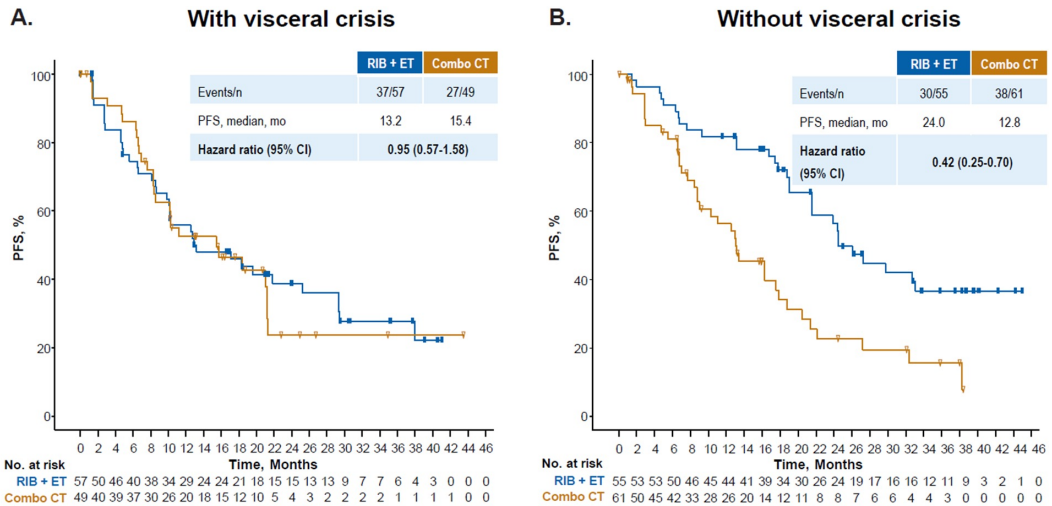
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- PROs

- Visceral crisis defined subjectively as severe organ dysfunction

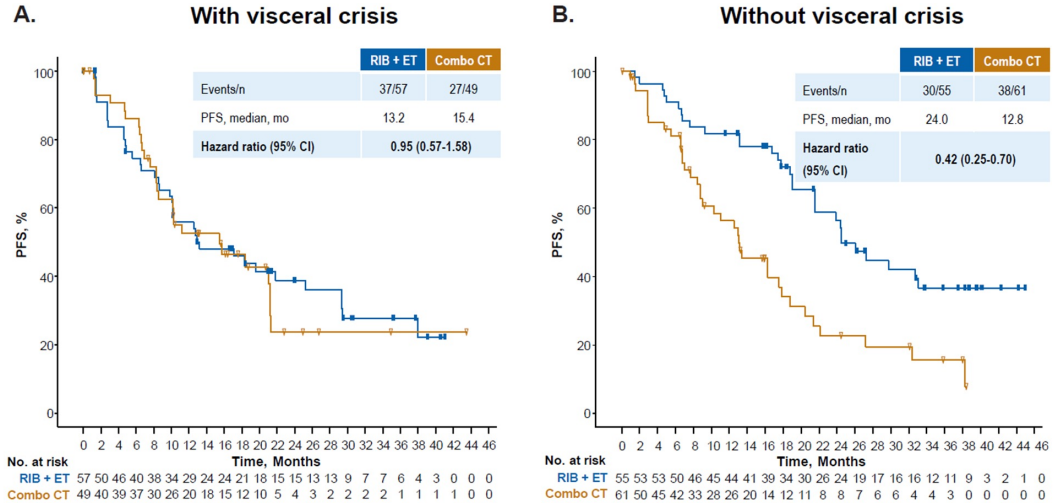
Azim HA, et al. ESMO 2023. Abstract 402P

RIGHT Choice (Phase 2, subgroup analysis): Efficacy

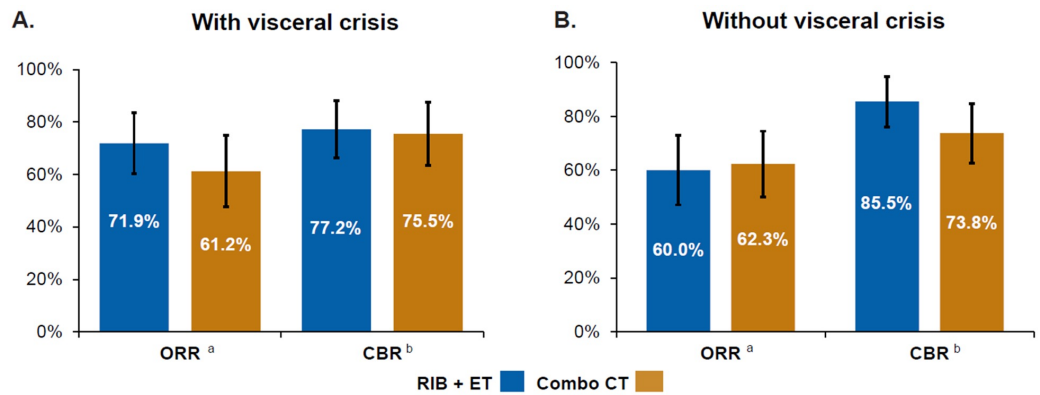
PFS



TTF



ORR and CBR



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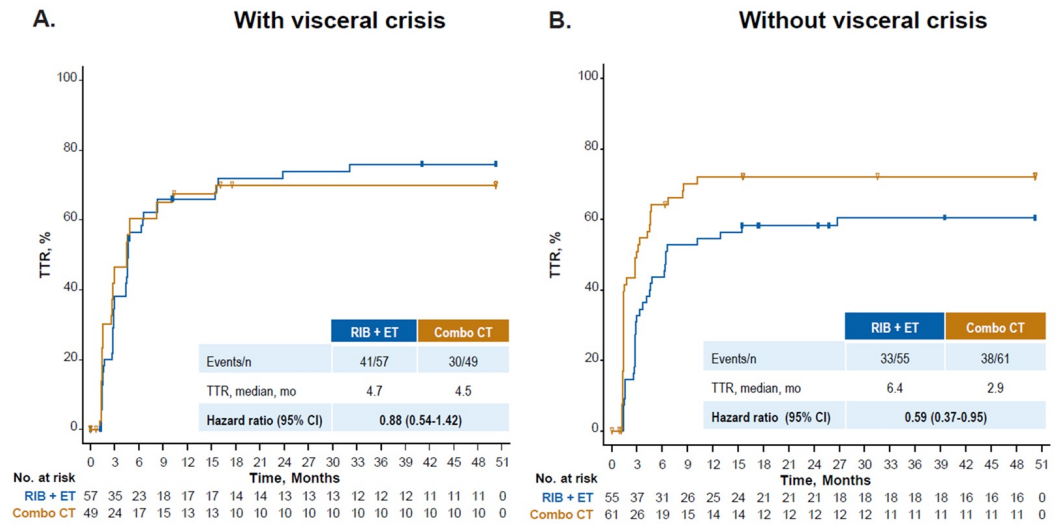


Azim HA, et al. ESMO 2023. Abstract 402P

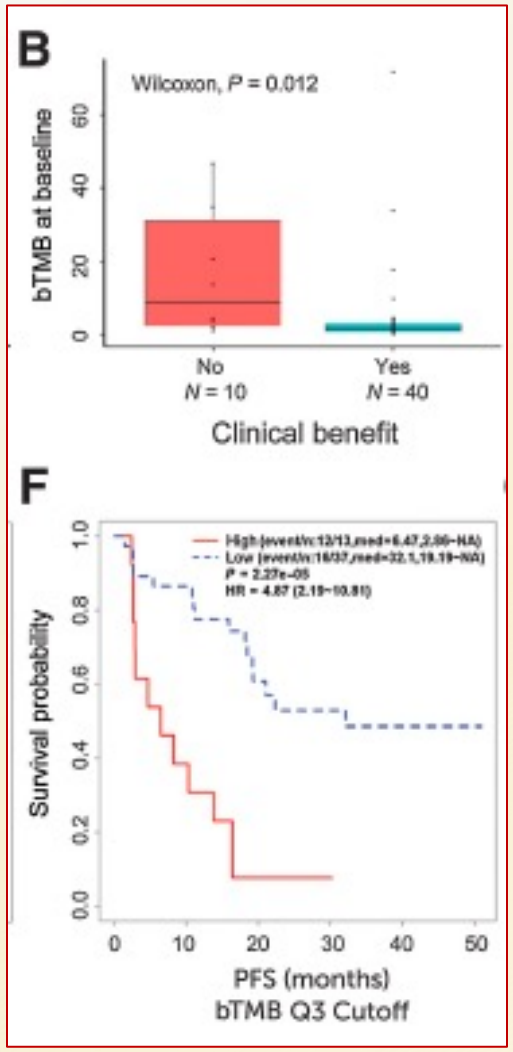
What About 2L CDKi Post-Progression on 1L CDKi?

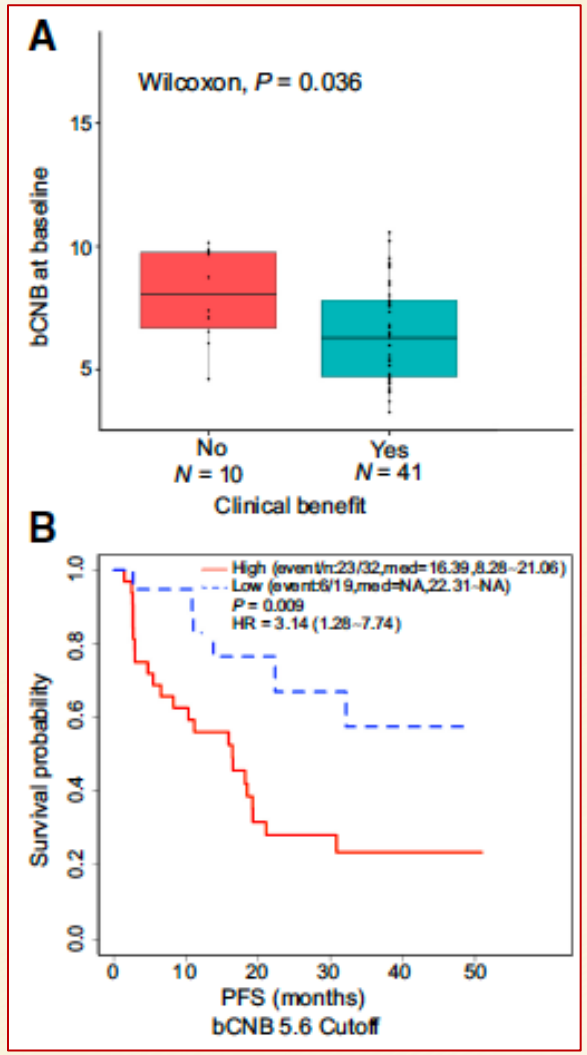
	MAINTAIN	PACE	PALMIRA
Patients (n)	120	166	198
1st line CDK4/6i	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
% 1st line CDK4/6i >12mo	67%	75%	86%
Endocrine therapy	Fulvestrant (83%) or exemestane	Fulvestrant (100%)	Fulvestrant (90%) or letrozole
'Continuation' CDK4/6i	Ribociclib	Palbociclib	Palbociclib
PFS ET only	**2.8mo**	**4.8mo**	**3.6mo**
PFS Fulv + CDK4/6i	**5.3mo**	**4.6mo**	**4.9mo**

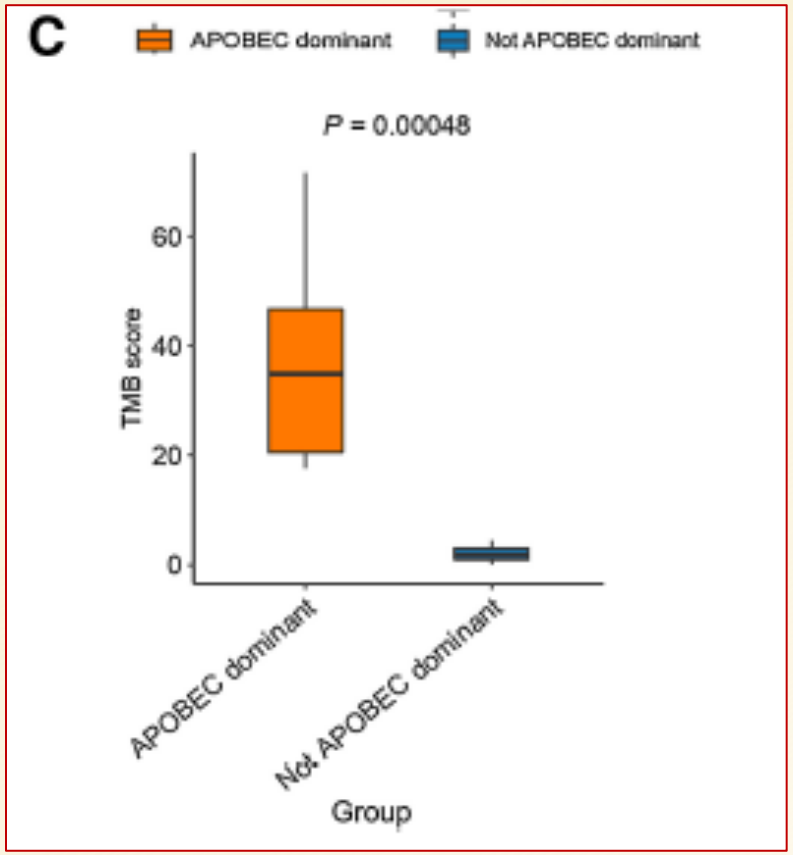
Different studies, different designs, different study populations, different subgroup definitions

Kalinsky *JCO* 2023; Mayer *SABCS* 2022; Llombart-Cussac *ASCO* 2023

Genomic complexity at baseline reflected by APOBEC mutational signature and high blood tumor mutational burden (bTMB) and copy number burden (bCNB) is prognostic for resistance to CDK4/6 inhibitors





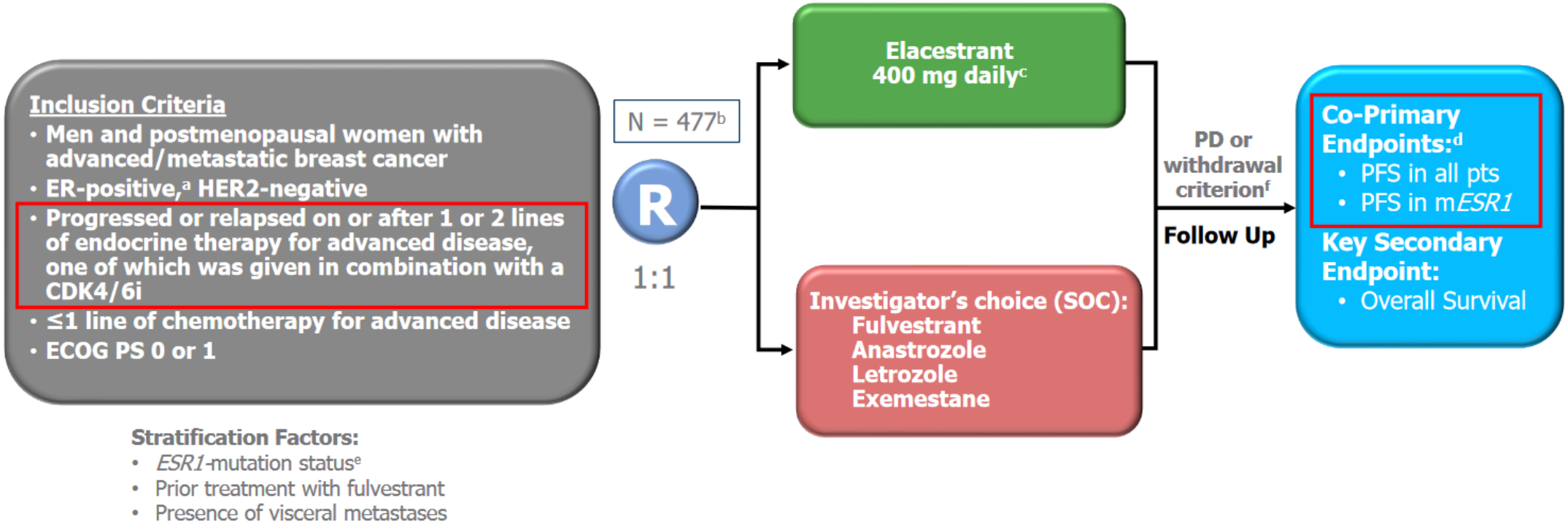


High bTMB associated with ABOPEC mutational signatures

Davis et al. Clin Cancer Res 2023 (PMID: 36693175)

EMERALD: Elacestrant vs ET in post CDK4/6i Setting

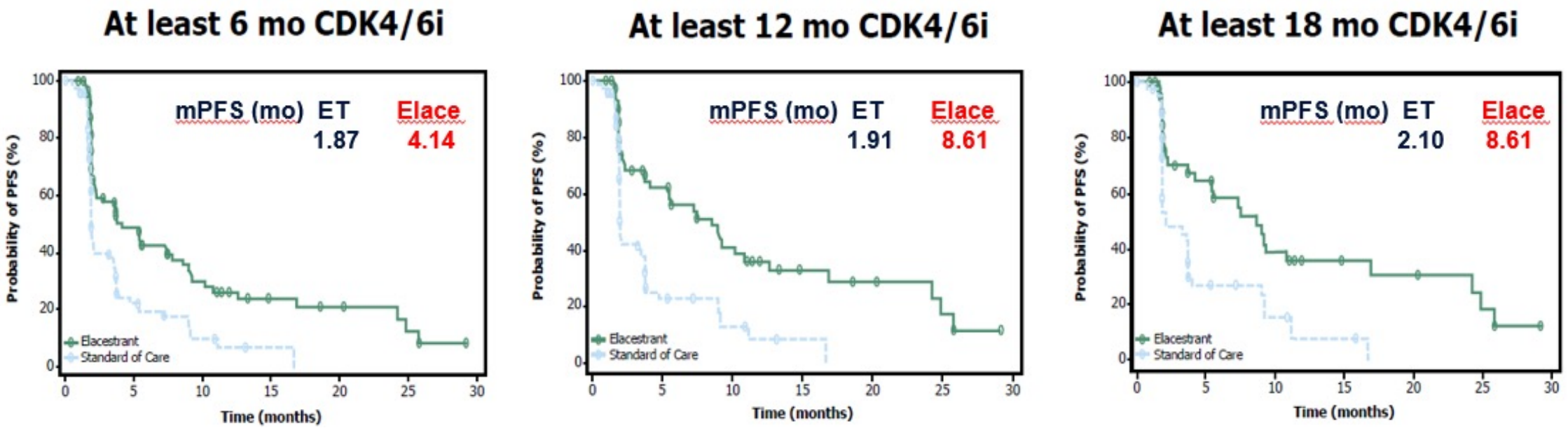
- Elacestrant is an oral selective estrogen receptor degrader (SERD)



Patient population:
Prior CDK 4/6i (100%)
Prior fulvestrant (30%)

EMERALD - Patients with *ESR1*-mut tumors PFS by duration of CDK4/6i

ESR1 MUTANT



ESR1 Mutations in ctDNA Found after Progression on AI+ CDK 4/6 Inhibitor

Most AEs including nausea were G1 or G2; no G4 treatment-related AEs

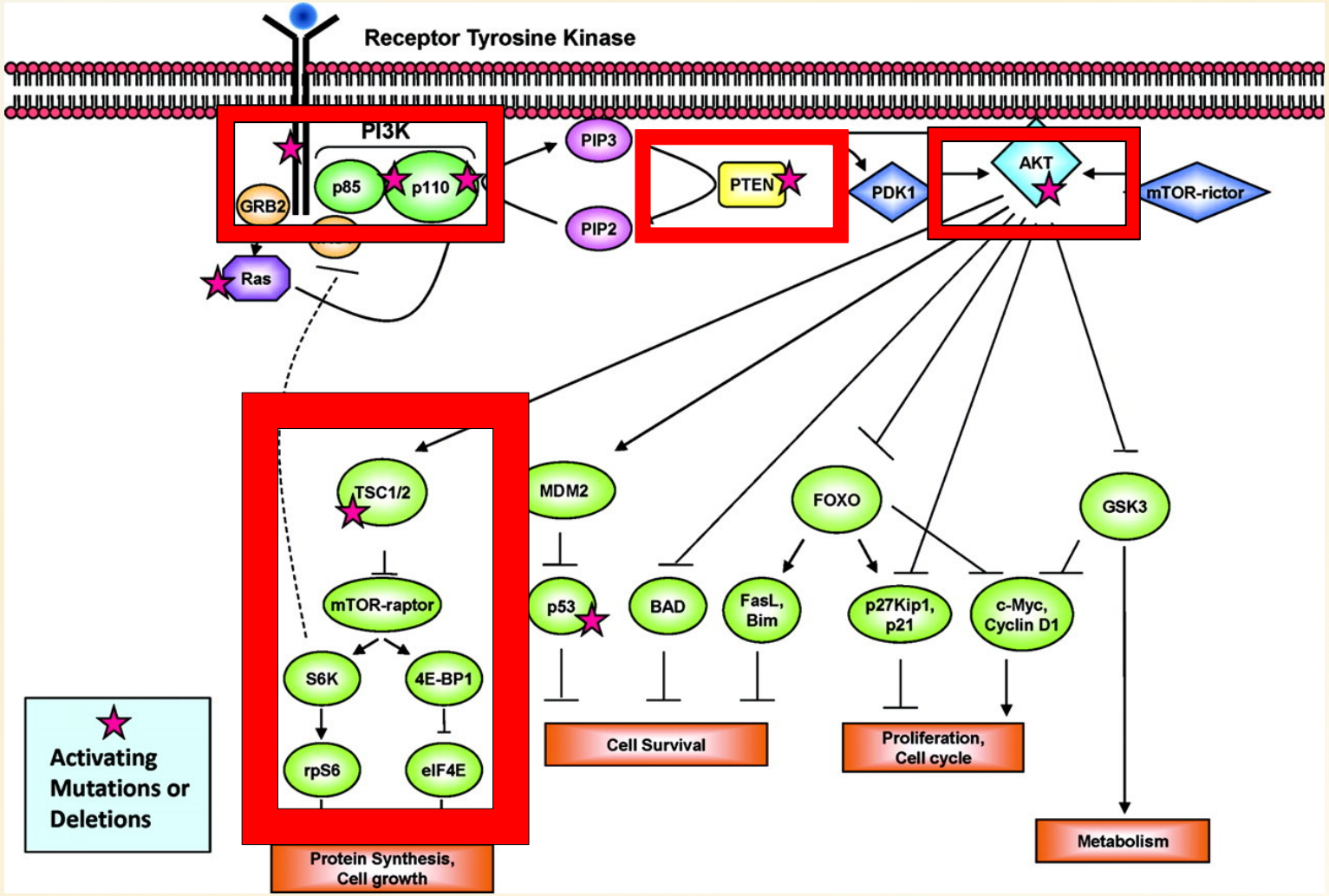
✓ Elacestrant is FDA approved for patients with ER+/HER2- and ESR1-mutated MBC following PD on at least 1 line of endocrine therapy (Jan 27, 2023)

Guardant360 CDx assay approved as companion diagnostic to identify eligible patients

- 48% pts in EMERALD had ESR1 mutation <u>following</u> CDK4/6 inhibitor therapy, mainly with an AI
- 1L PADA1 trial showed 3.2% pts <u>beginning</u> AI + CDK4/6 inhibitor had ESR1 (Pradines A, et al. Cancer Res supp, AACR, 2021)

PI3K/AKT/M-TOR Pathway

Most commonly dysregulated pathway in breast cancer



Baselga J, et al. The Oncologist 2011 (PMID: 21278436)

PFS Benefit of Alpelisib in 2L post progression after CDK4/6i:5-7 mos

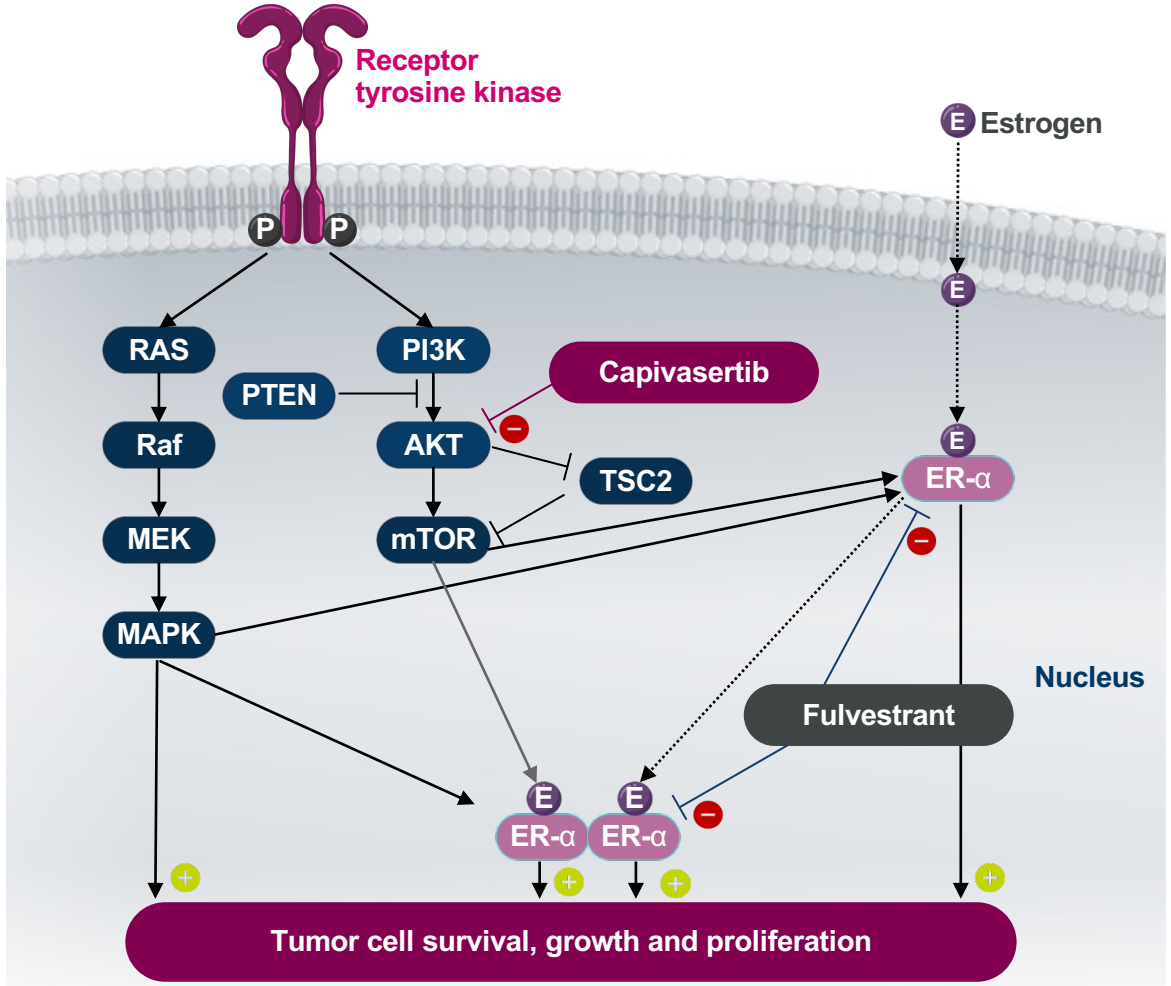
	BYLieve: PI3Ki + ET in HR+/HER2- BC With PIK3CA Mutation and PD on CDK4/6i		
	Cohort A[1] (n = 121)	Cohort B[2] (n = 115)	Cohort C[3] (n = 126)
Cohort population	CDK4/6i + AI as immediate prior tx	CDK4/6i + fulvestrant as immediate prior tx	Chemo or ET as immediate prior tx
Endocrine partner	Fulvestrant	Letrozole	Fulvestrant
PI3Ki	Alpelisib	Alpelisib	Alpelisib
Median PFS, mo	7.3	5.7	5.6
▪ HR (PI3Ki vs control)	NA	NA	NA

Rugo. Lancet Oncol. 2021;22:489.
Rugo. SABCS 2021. PD2-07.
Rugo. SABCS 2020. Abstr PD13-05.

Background and overview of capivasertib

- AKT pathway activation in HR+/HER2– MBC through alterations in *PIK3CA, AKT1 and PTEN*, but may also occur in cancers without those genetic alterations.[1,2] AKT signalling is implicated in the development of resistance to endocrine therapy[2]

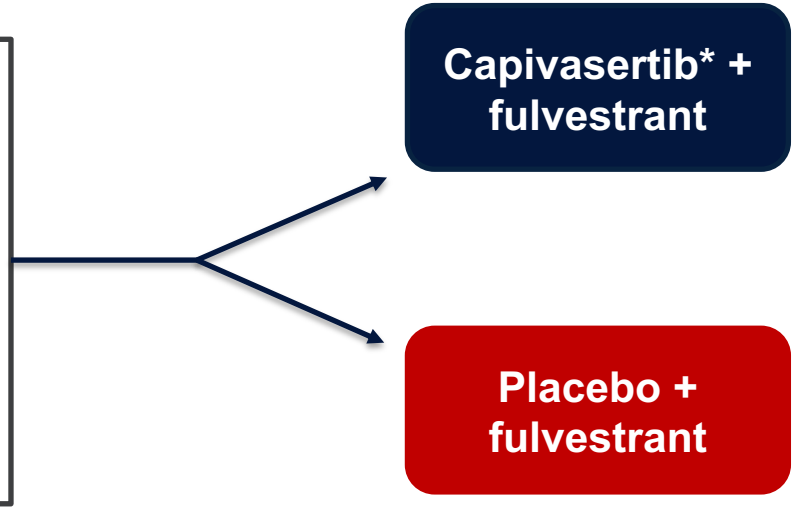
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)



1. Millis et al. *JAMA Oncol* 2016;2:1565-1573; 2. Toss et al. *Oncotarget*. 2018;9:31606-31619; 3. Howell et al. *Lancet Oncol* 2022;23:851–64.

CAPItello-291: Phase 3 trial with capivasertib in ER+ MBC

- HR+ MBC with recurrence while on *or* within 12 months of adjuvant AI *or* PD on AI for MBC
- ≤2 lines of ET for MBC
- 0-1 prior chemo for MBC



*400mg BID daily,
4 days on, 3 days off

Patient population

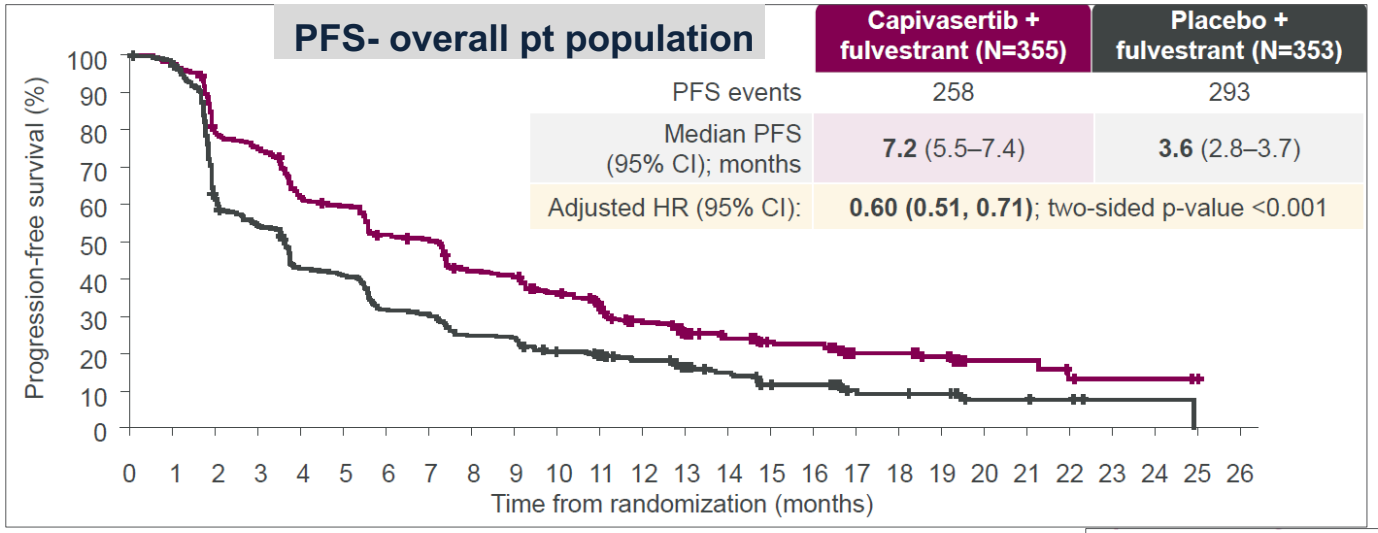
Visceral disease	66-73%
AKT pathway alterations	38-43%
Median priors for MBC	1
Prior CDK 4/6i	67-72%
Prior chemo for MBC	17-19%

Turner NC et al. SABCS 2022, GS3-04

CAPItello-291: Dual primary endpoints

PFS in overall population & AKT pathway altered population

PFS- overall pt population

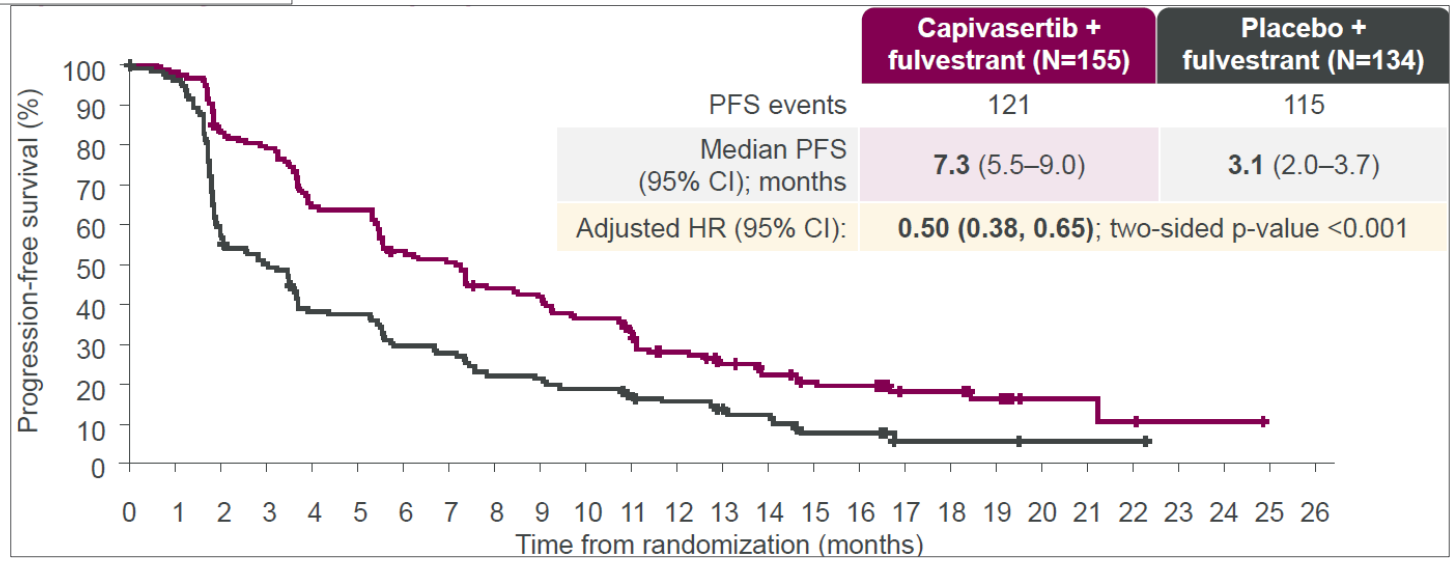


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

- Statistically significant and clinically meaningful improvement in in PFS in all patients regardless of AKT pathway alteration
- OS data is immature

Capivasertib + fulvestrant is likely to be an option for select patients following progression on ET (+/- CDK 4/6i)

PFS- AKT pathway altered pt population



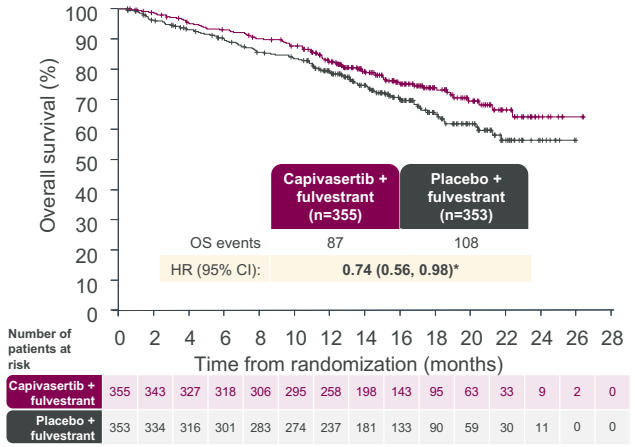
	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

Turner NC et al. SABCS 2022, GS3-04

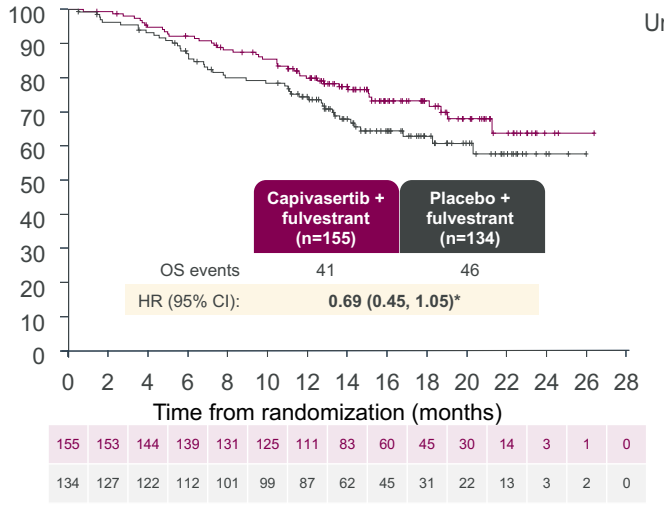
Overall Survival

- Overall survival immature at just 28% maturity
  - Less events in the Capi arm

Overall population

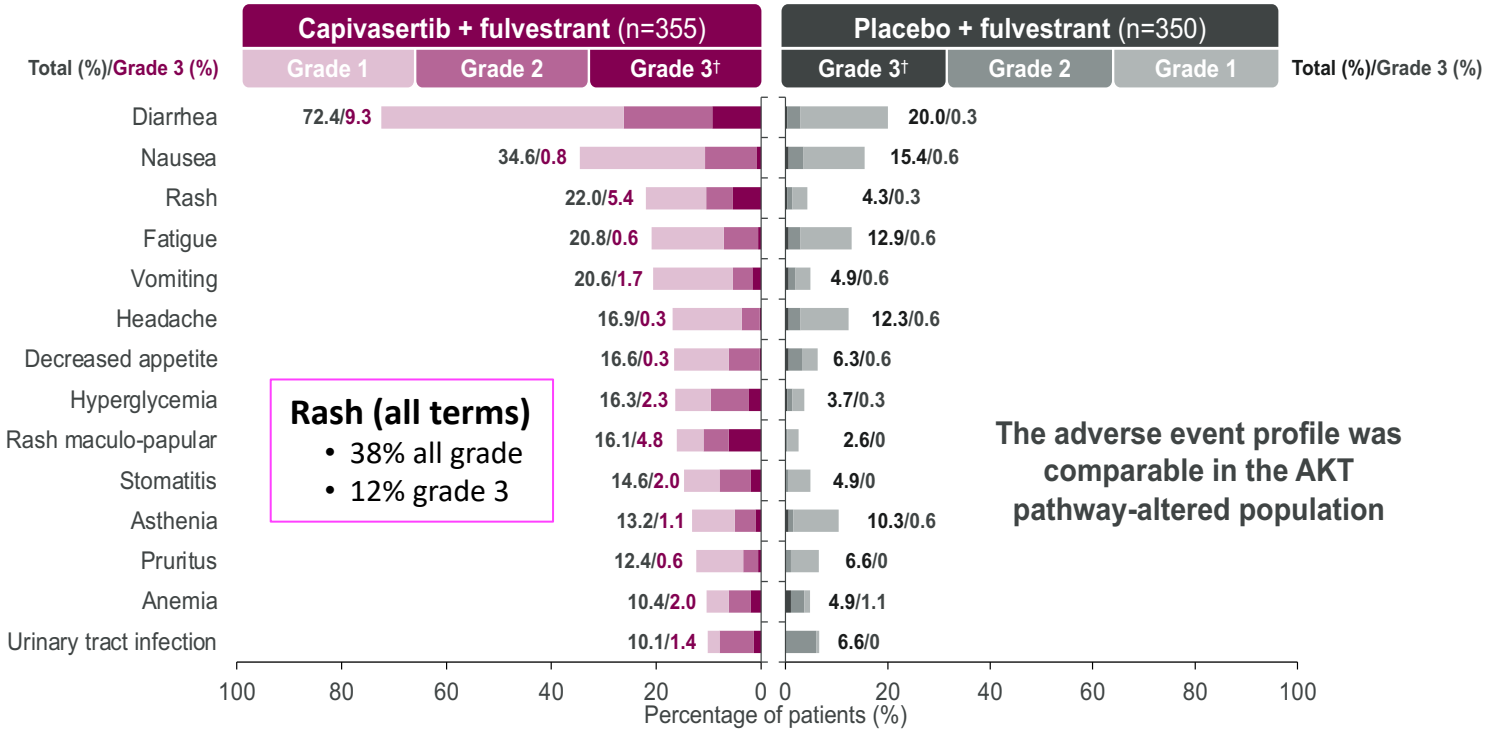


AKT pathway-altered population



Safety

Adverse events (>10% of patients) – overall population



Rash (all terms)
- 38% all grade
- 12% grade 3

The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

AEs leading to:

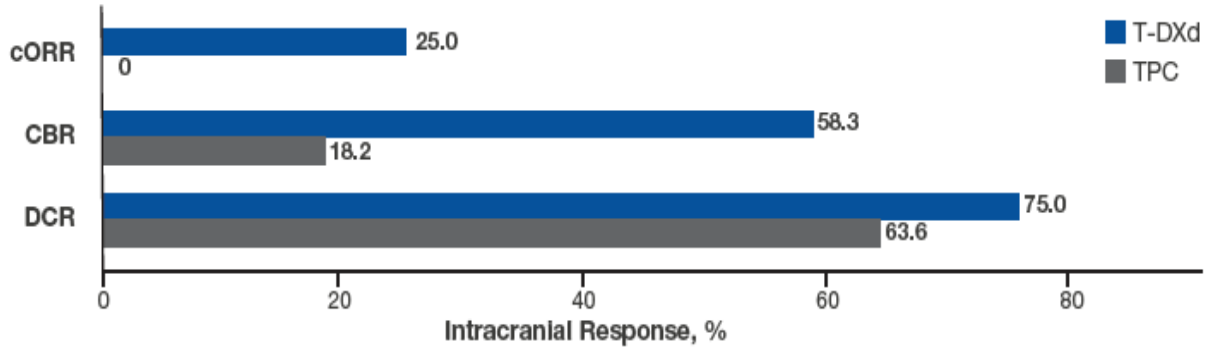
- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

Turner et al, SABCS 2022

DESTINY-Breast04 (Phase 3): Subgroup analysis of T-DXD vs TPC among patients with HER2-low metastatic breast cancer with brain metastases

- An open-label, multicenter study of T-DXd vs TPC among patients HER2-low unresectable and/or metastatic breast cancer

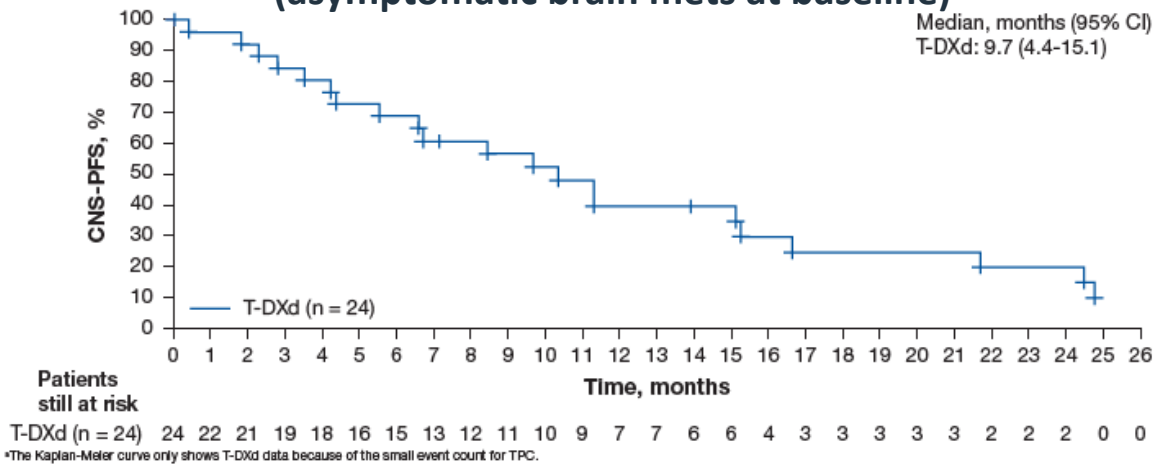
Intracranial response (asymptomatic brain mets at baseline)



	Best Overall Intracranial Response	
n (%)	T-DXd (n = 24)	TPC (n = 11)
CR[a]	4 (16.7)	0
PR[a]	2 (8.3)	0
SD	12 (50.0)	7 (63.6)
PD	0	1 (9.1)
Not evaluable (NE)	1 (4.2)	0
Missing[b]	5 (20.8)	3 (27.3)

[a]Confirmation was required for CR and PR. [b]Data were not available for analysis.

CNS-PFS among patients treated with T-DXd (asymptomatic brain mets at baseline)



*The Kaplan-Meier curve only shows T-DXd data because of the small event count for TPC.

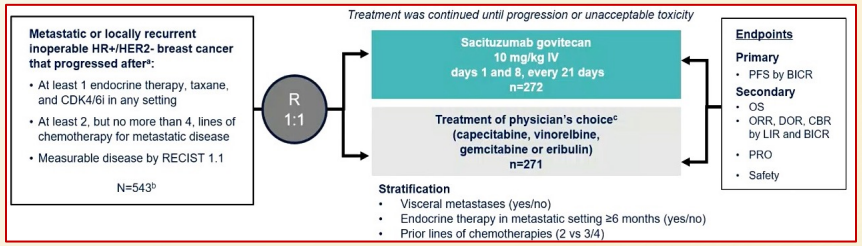
Sites of first progression (asymptomatic brain mets at baseline)

n (%)	T-DXd (n = 24)	TPC (n = 11)
Patients with progression	17 (70.8)	7 (63.6)
Sites of first progression		
Intracranial only	2 (8.3)	3 (27.3)
Extracranial only	15 (62.5)	4 (36.4)

TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.

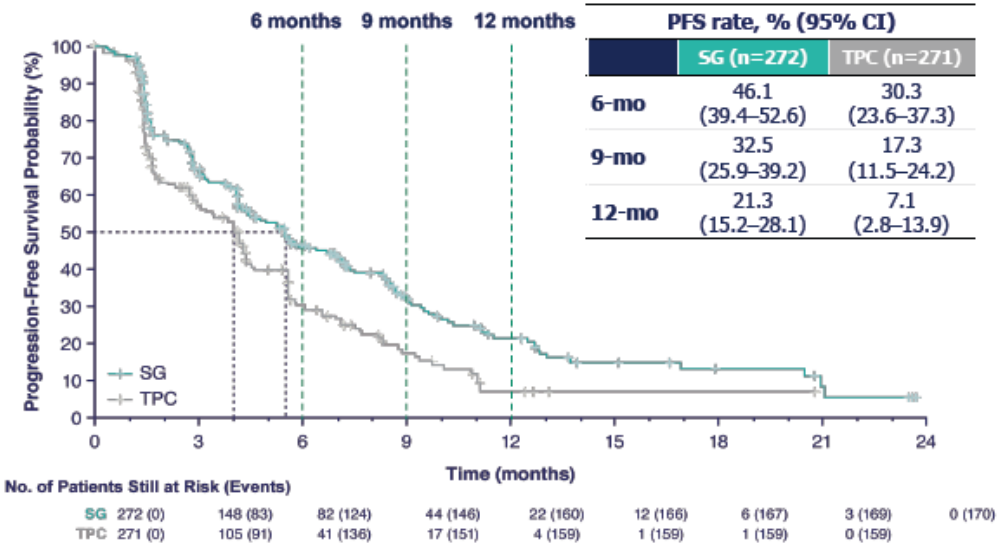
Tsurutani J, et al. ESMO 2023. Abstract 388P

TROPICS-02: Phase III Trial Sacituzumab Govitecan vs. TPC in ER+ MBC



PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



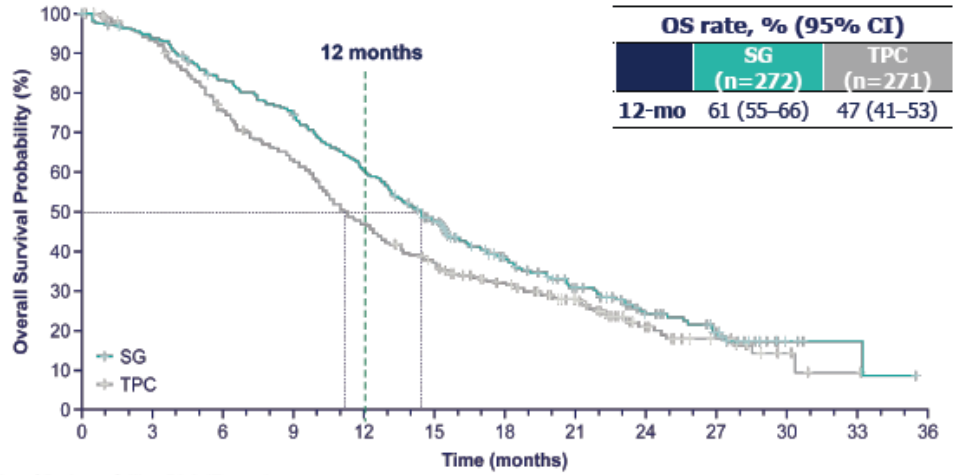
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

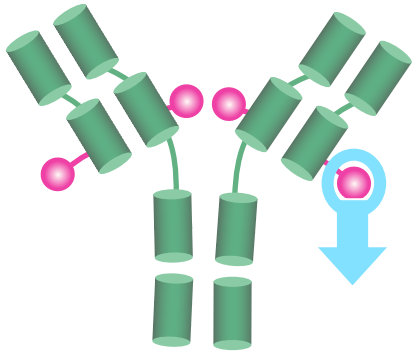
SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Rugo et al. ESMO 2022 (LBA76); Rugo et al. Lancet 2023 (PMID: 37633306)

Background: Dato-DXd

- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[1] and has several unique properties*:
  - Optimised drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumour-selective cleavable linker
  - Bystander antitumour effect
- Dato-DXd previously demonstrated **promising antitumour activity** and a **manageable safety profile** with a convenient Q3W schedule in pre-treated patients with **metastatic HR+/HER2– breast cancer**[2]

Dato-DXd: Humanised anti-TROP2 IgG1 monoclonal antibody



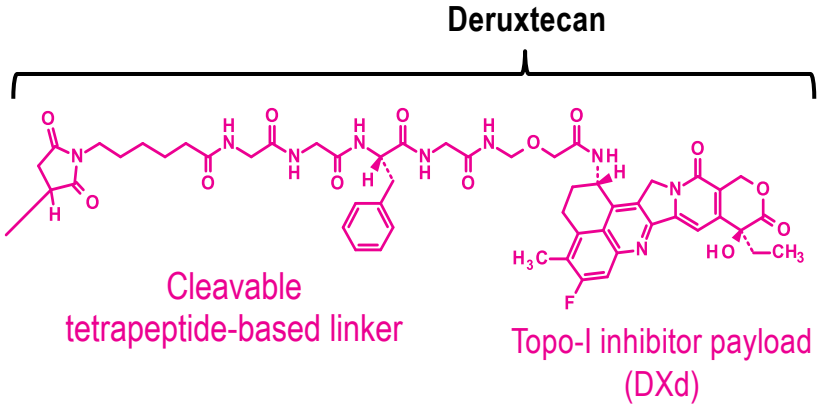


Image is for illustrative purposes only; actual drug positions may vary.

*The clinical relevance of these features is under investigation. Based on animal data.
Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; Q3W, every 3 weeks; Topo-I, topisomerase I.

1. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40;
2. Meric-Bernstam F, et al. Poster presentation at SABCS 2022: abstract PD13-08.

TROPION-Breast01 Study Design[1]

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W. BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world.

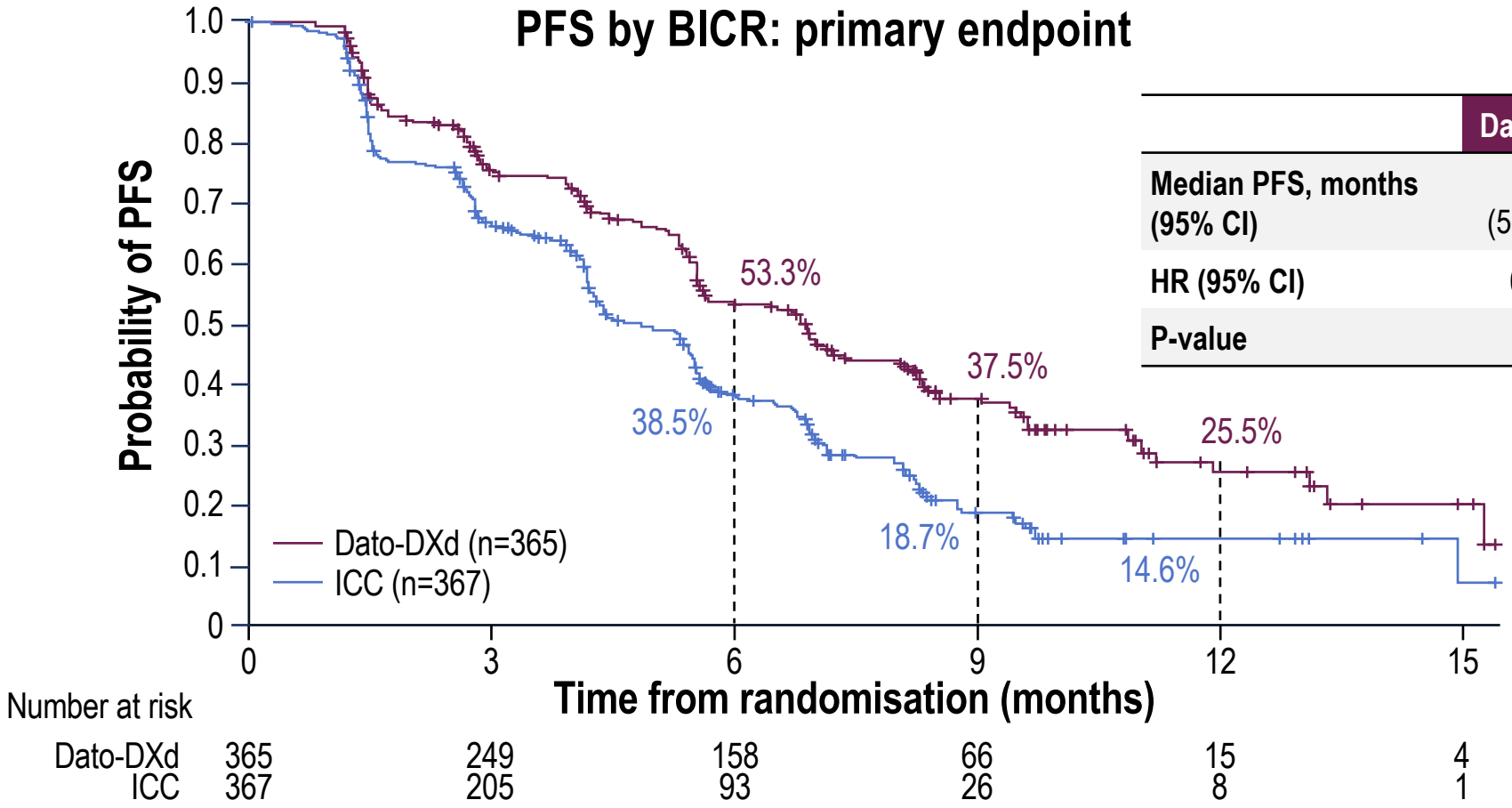
1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Demographics and Baseline Characteristics

		Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years		56 (29–86)	54 (28–86)
Female, n (%)		360 (99)	363 (99)
Race, n (%)	Black or African American / Asian / White / Other*	4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%)	Hispanic or Latino / Not Hispanic or Latino†	40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy,‡ n (%)	1 / 2	229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%)	Yes / No	299 (82) / 66 (18)	286 (78) / 81 (22)
Prior taxane and/or anthracycline, n (%)	Taxane and/or Anthracycline	330 (90)	339 (92)
	Neither	35 (10)	28 (8)

*Including not reported. †Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group.
‡In the inoperable/metastatic setting; one patient in the Dato-DXd group had 3 prior lines of chemotherapy; one patient in the ICC group had 4 prior lines.

Progression-Free Survival



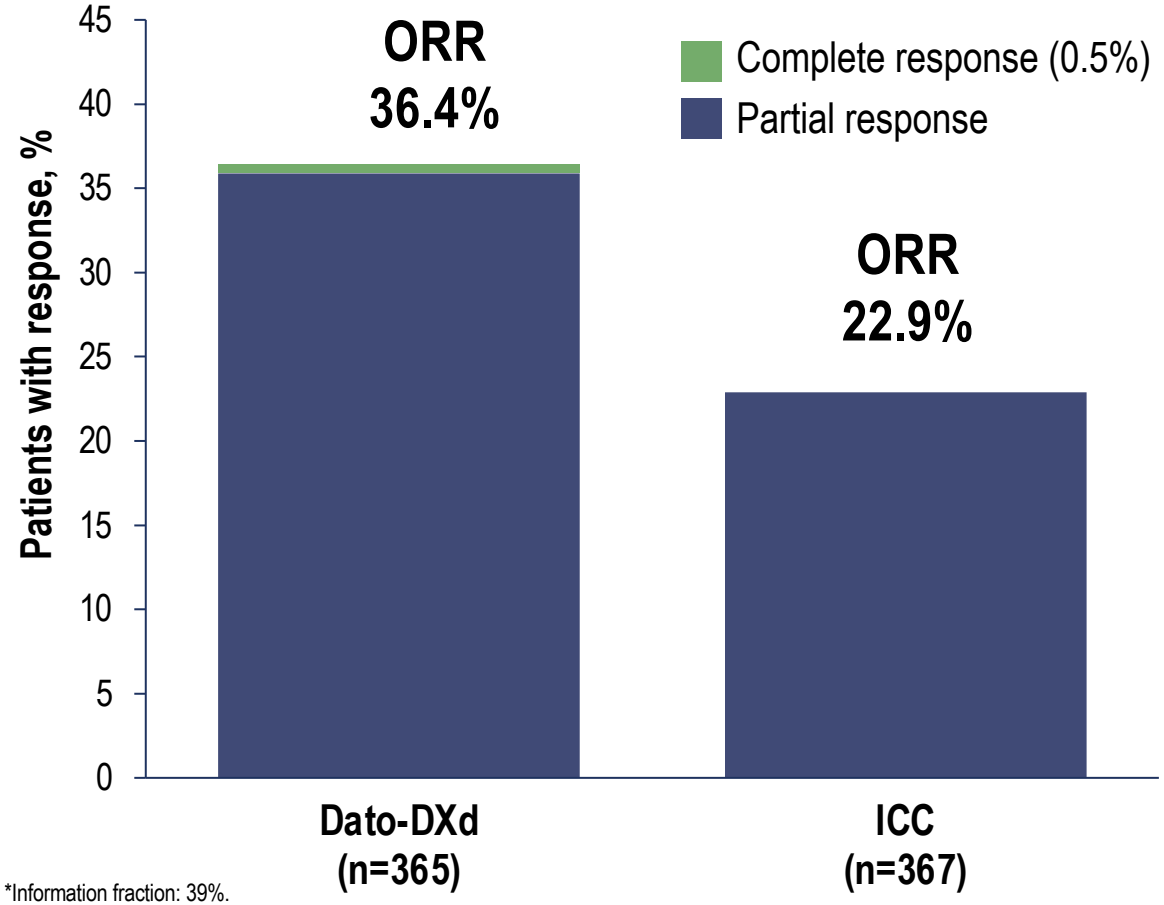
	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	**0.63 (0.52–0.76)**	
P-value	<0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

CI, confidence interval; HR, hazard ratio

Response and Interim OS

Response Rate



*Information fraction: 39%.
ORR, confirmed objective response rate by BICR

OS: Dual Primary Endpoint

- OS data not mature:*
  - Median follow-up 9.7 months
- A trend favouring Dato-DXd was observed:
  - HR 0.84 (95% CI 0.62–1.14)
- The study is continuing to the next planned analysis for OS

TRAEs Occurring in ≥15% of Patients and AESIs

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

- Most TRAEs were grade 1–2 and manageable

AESIs

- Oral mucositis/stomatitis:† led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events:‡ most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD:§ rate was low; mainly grade 1/2

Adjudicated drug-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)¶	0

*Neutropenia included the PTs neutropenia and neutrophil count decreased. †Oral mucositis/stomatitis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC. ‡Ophthalmologic assessments were required at screening, and then every 3 cycles from C1D1 and at end of therapy; ocular events included selected PTs from Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis), 0% with ICC. §ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). ¶One adjudicated drug-related grade 5 ILD event: attributed to disease progression by investigator. ILD, interstitial lung disease; PTs, preferred terms; SMQ, standard MedDRA query; SOC, system organ class.

Destiny-Breast 03: TdX vs. T-DM1 as Second–Line Therapy for HER2+ MBC

DESTINY-Breast03: Study Design

An open-label, multicenter, phase 3 study (NCT03529110)

Patients
- Unresectable or metastatic HER2 positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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)
- T-DM1 3.6 mg/kg Q3W (n = 263)

Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

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

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.
Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

Daiichi-Sankyo | AstraZeneca

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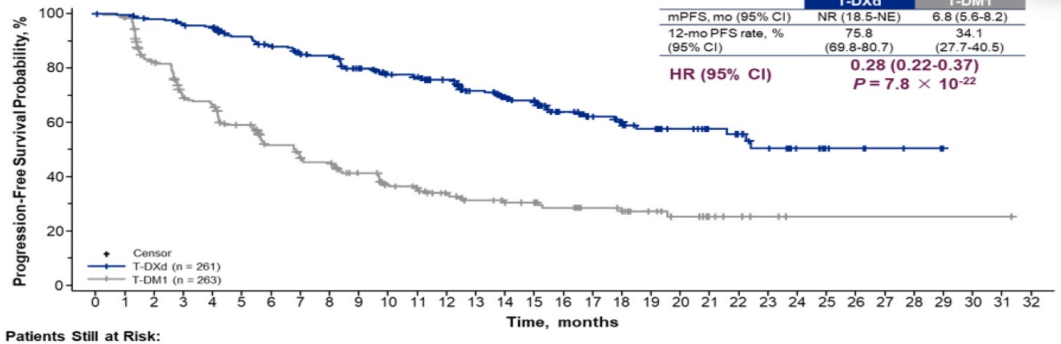
DESTINY-Breast03: May 21, 2021 DCO

Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37) $P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

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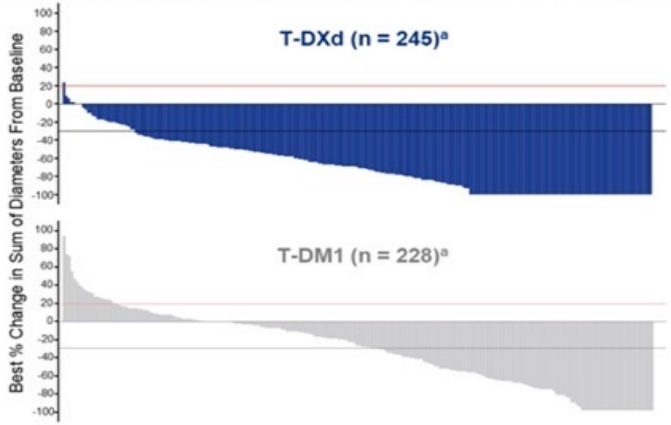
DESTINY-Breast03: May 21, 2021 DCO

Confirmed ORR and Best Overall Response



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b] [95% CI]	208 **(79.7)** [74.3-84.4]	90 **(34.2)** [28.5-40.3]
	$P < .0001$	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

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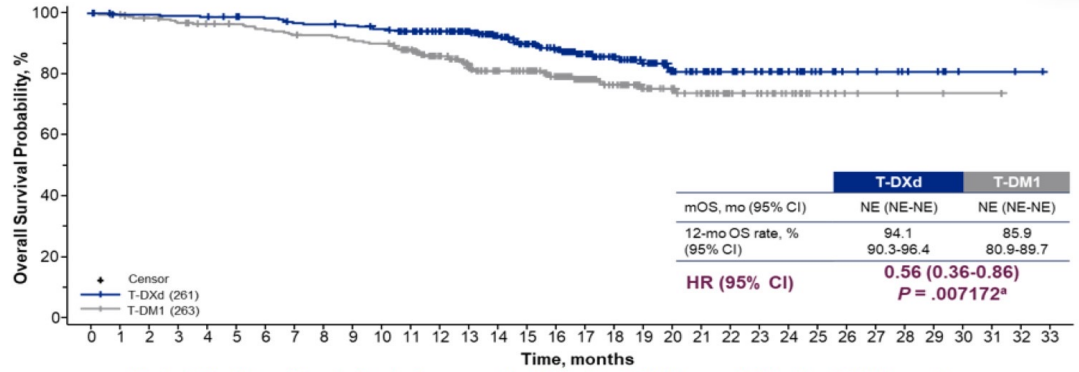
DESTINY-Breast03: May 21, 2021 DCO

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	0.56 (0.36-0.86) $P = .007172$[a]	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]$P = .007172$, but does not cross pre-specified boundary of $P < .000265$

Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

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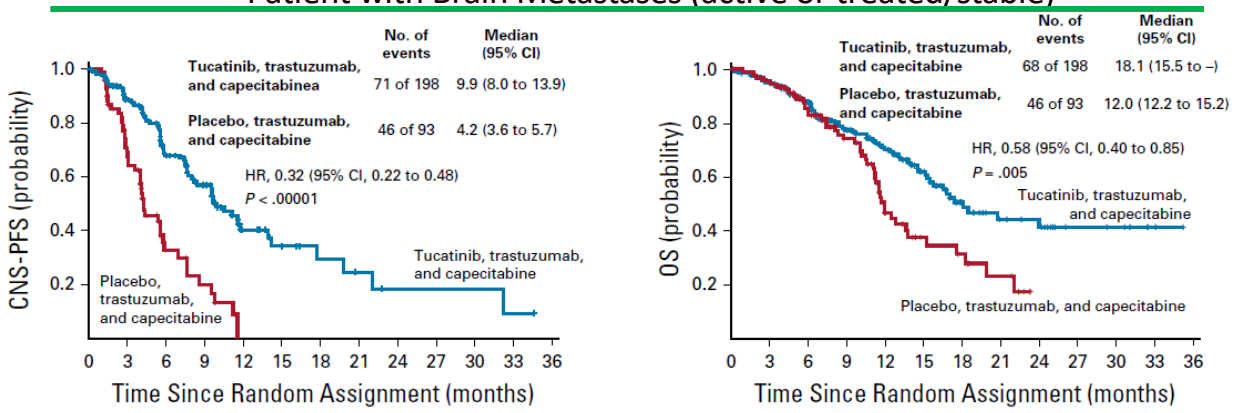
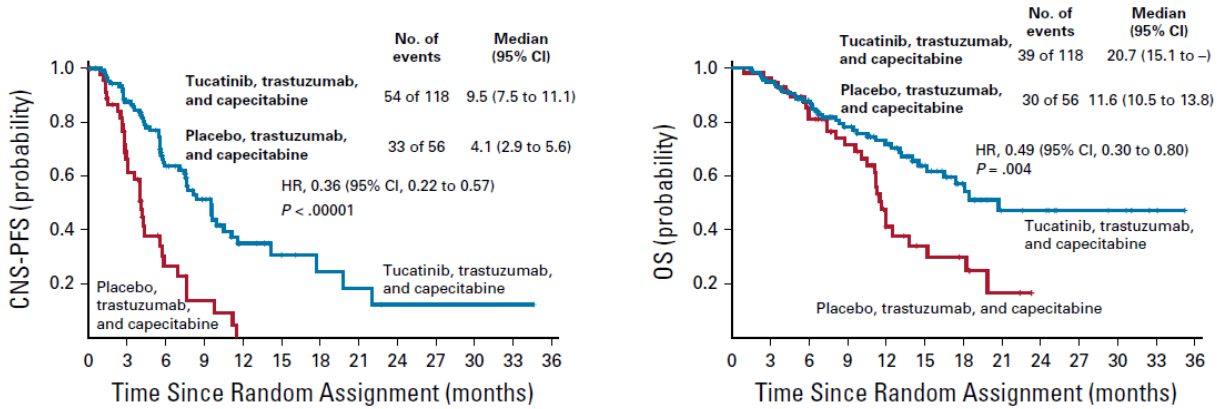
Cortes et al. NEJM 2022 (PMID: 35320644)

Intracranial CNS-Specific Outcomes: HER2CLIMB Study Results

Patient with Brain Metastases (active or treated/stable)



Patient with Brain Metastases (active)

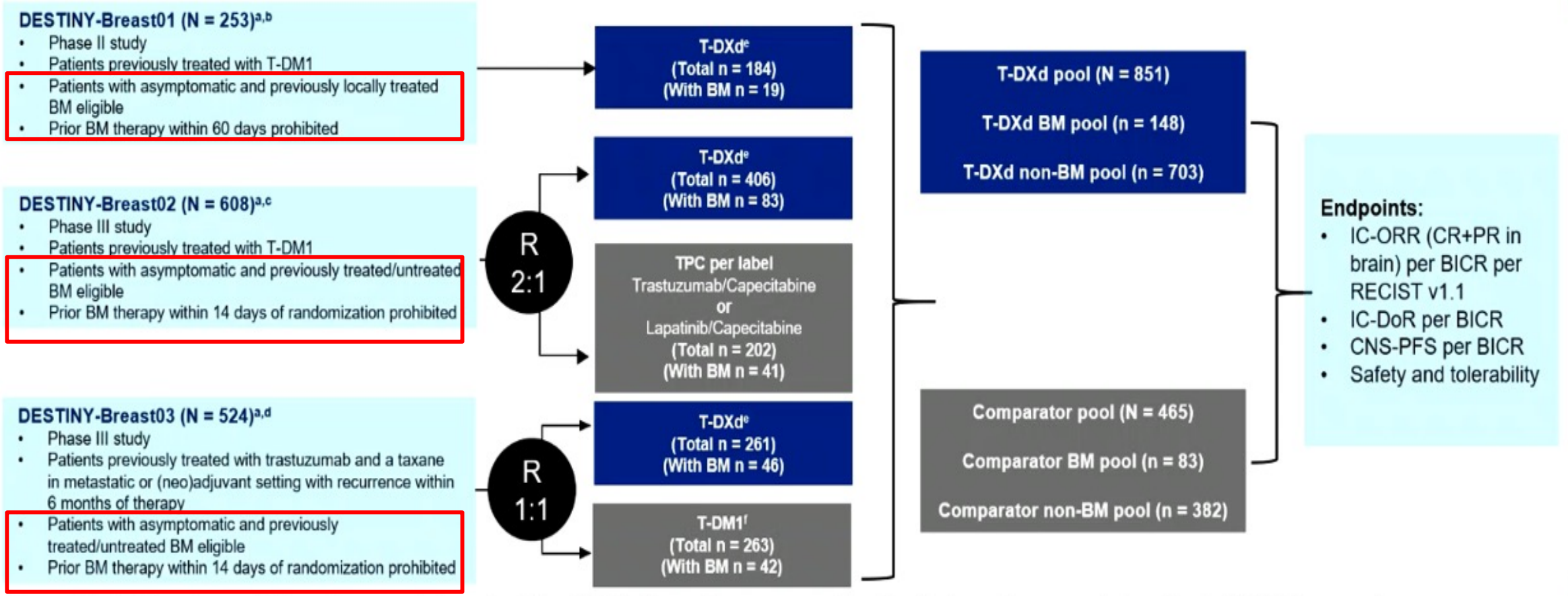


Intra-Cranial CNS Response (RECIST) N=75	Tucatinib N=55 N (%)	Placebo N=20 N (%)
CR	3 (5.5)	1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not Available	3 (5.5)	0
Confirmed ORR	26 (47.3)	4 (20.0)
95% CI	33.7-61.2%	5.7-43.7%
Stratified p-value	0.03	
DOR (months)	6.8	3.0

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; ORR=objective response rate (CR+PR); DOR=duration of intracranial response

Lin NU, et al. *J Clin Oncol*. 2020;38(23):2610-2619.

DESTINY-Breast-01/-02/-03 pooled analysis: T-DXd among patients with HER2+ metastatic breast cancer with brain metastases



- **The BM and non-BM pools were determined by BICR at baseline among all patients based on mandatory brain CT/MRI screening**

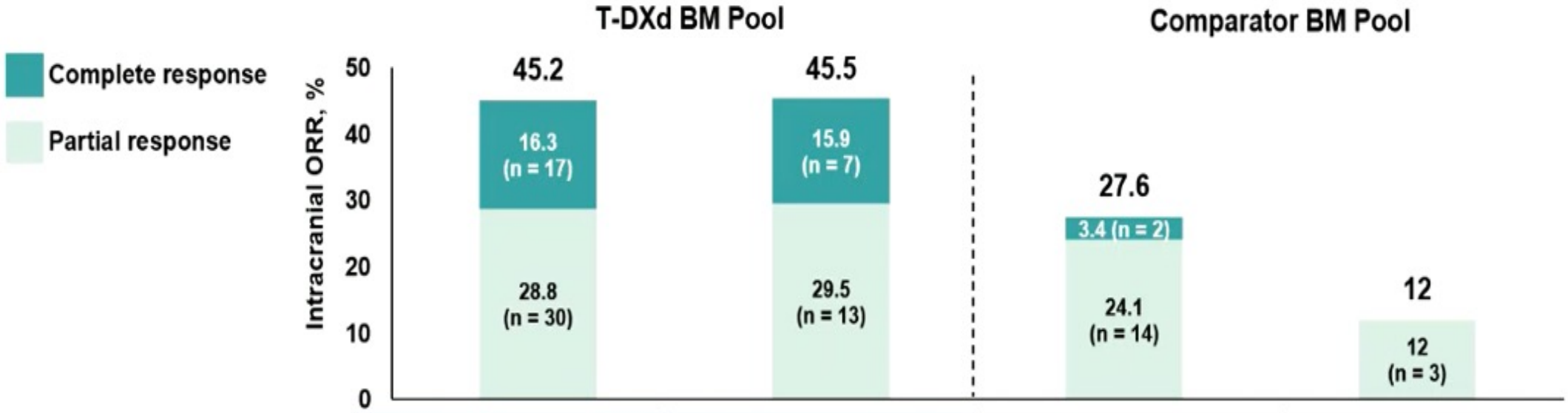
- Per FDA criteria, patients with untreated BMs from DESTINY-Breast02 and -03 would be considered to have active BMs[5]
  - The population of patients with baseline BMs from DESTINY-Breast02 and -03 therefore consists of a mix of treated/stable and untreated/active metastases

T-DXd, trastuzumab deruxtecan.

Hurvitz S, et al. ESMO 2023. Abstract 377C

DESTINY-Breast-01/-02/-03 pooled analysis: T-DXd efficacy among patients with HER2+ metastatic breast cancer with brain metastases

Intracranial ORR[a]



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

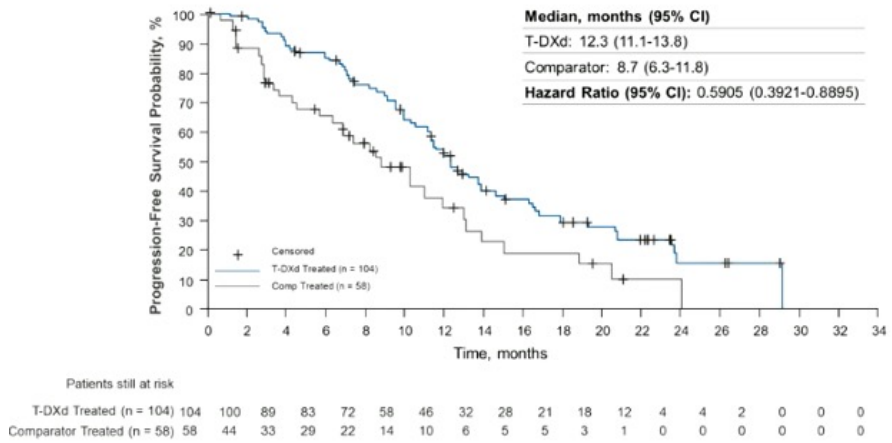
T-DXd, trastuzumab deruxtecan.

Hurvitz S, et al. ESMO 2023. Abstract 377O

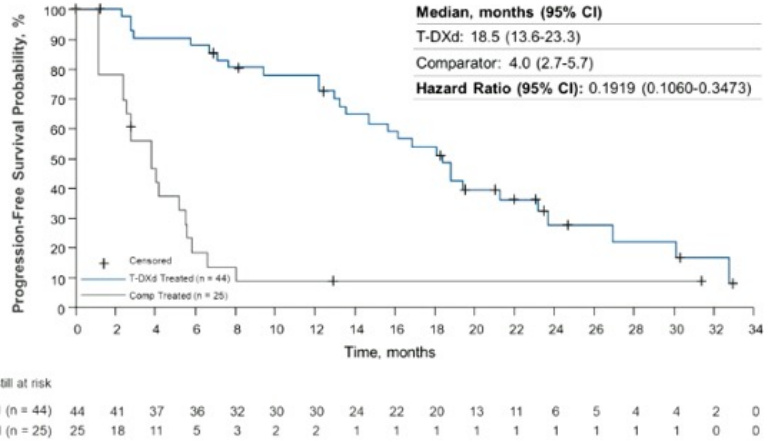
DESTINY-Breast-01/-02/-03 pooled analysis: T-DXd efficacy among patients with HER2+ metastatic breast cancer with brain metastases

CNS-PFS per BICR

Treated/Stable BMs



Untreated/Active BMs



Site of first progression per BICR

	T-DXd Pool (N = 851)		Comparator Pool (N = 465)	
	BM Pool (n = 148)	Non-BM Pool (n = 703)	BM Pool (n = 83)	Non-BM Pool (n = 382)
Patients with PD, n (%)	88 (59.5)	291 (41.4)	49 (59.0)	244 (63.9)
Site of first progression				
Intracranial only	38 (25.7)	16 (2.3)	13 (15.7)	6 (1.6)
Extracranial only	47 (31.8)	270 (38.4)	31 (37.3)	237 (62.0)
Both	3 (2.0)	2 (0.3)	5 (6.0)	0
Missing	0	3 (0.4)	0	1 (0.3)

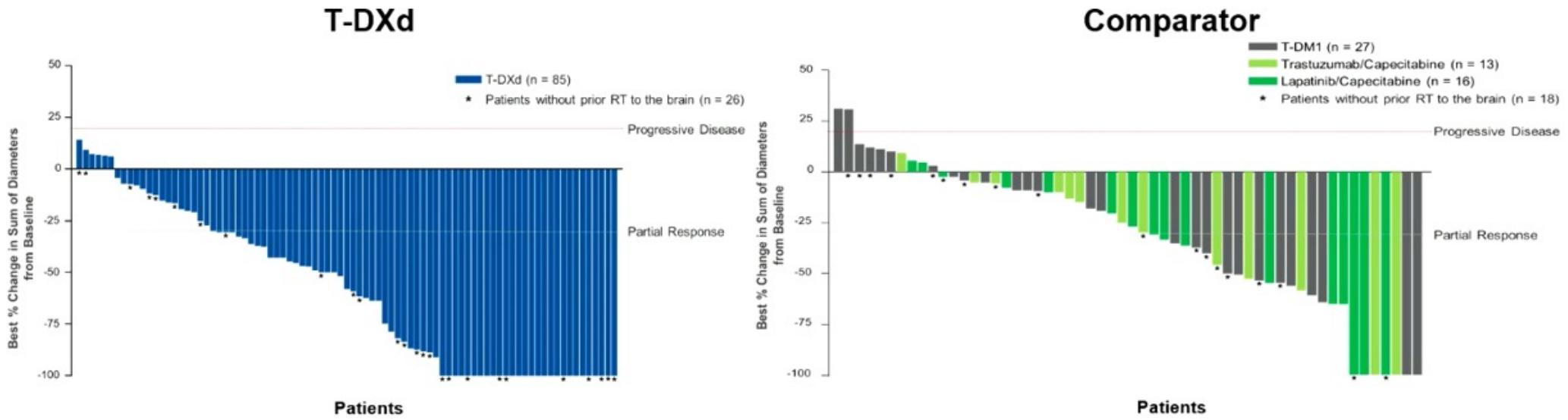
- **Rates of any PD were comparable in patients in both BM pool populations**

T-DXd, trastuzumab deruxtecan.

Hurvitz S, et al. ESMO 2023. Abstract 377O

DESTINY-Breast-01/-02/-03 pooled analysis: T-DXd among patients with HER2+ metastatic breast cancer with brain metastases

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**

T-DXd, trastuzumab deruxtecan.

Hurvitz S, et al. ESMO 2023. Abstract 377O

DESTINY-PanTumor01 (Phase 2): T-DXd among patients with solid tumors harboring specific HER2-activating mutations

- HER2 mutations occur in 2-3% of breast cancers
- In a Phase 1 study, T-DXd demonstrated anti-tumor activity in patients with tumors harboring HER2m, with confirmed responses in 9 of 19 patients

Key eligibility criteria
- Patients with unresectable and/or metastatic solid tumors with locally determined prespecified HER2m
- Progression after prior treatment or with no satisfactory alternative treatment options
- Prior HER2-targeting therapy allowed

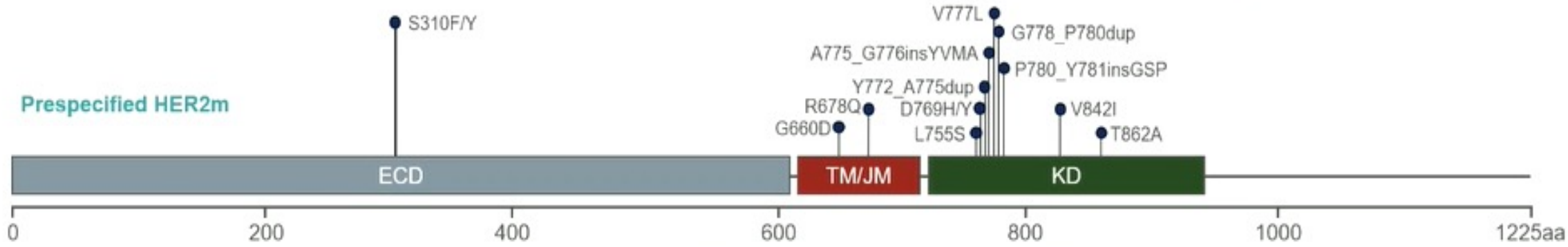
Key exclusion criteria
- HER2-positive (IHC 3+ or IHC 2+/ISH+) breast, gastric, or gastroesophageal junction cancer or HER2-mutant NSCLC
- History of non-infectious ILD/pneumonitis, current ILD, or suspected ILD that cannot be ruled out by imaging at screening

T-DXd
5.4 mg/kg
Q3W

Approx 100 participants
(max 20 per tumor type)

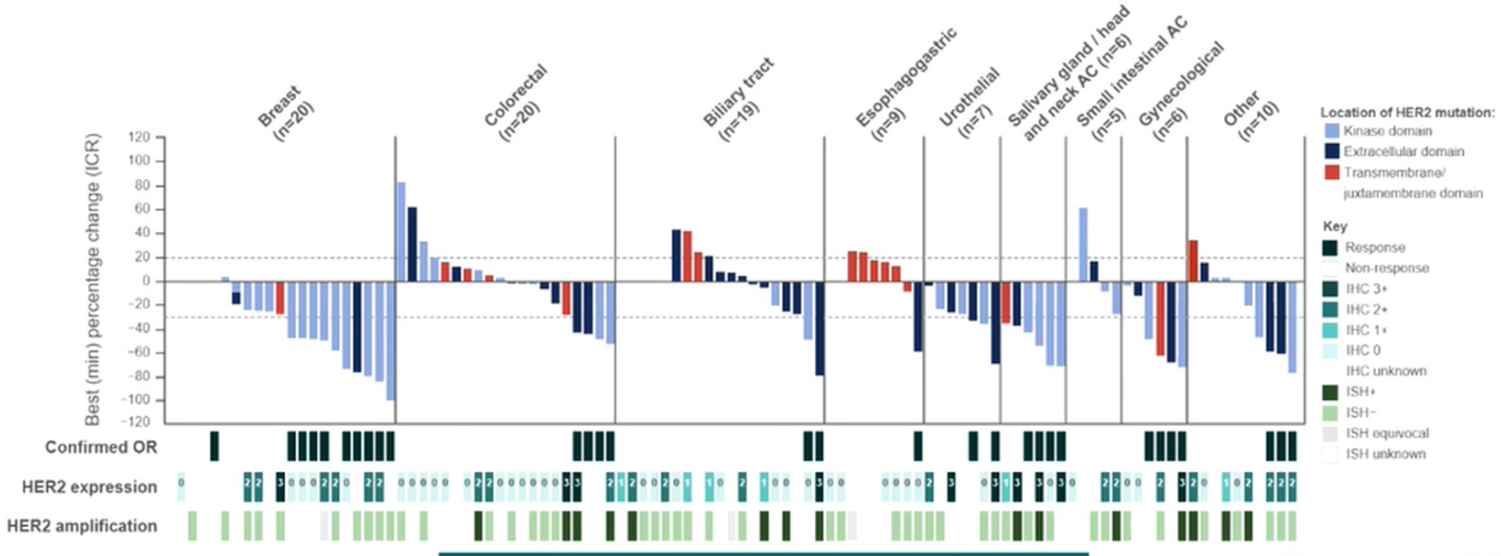
Primary endpoint
- Confirmed ORR (ICR)

Secondary endpoint
- DOR
- DCR
- Confirmed ORR (investigator assessed)
- PFS
- OS
- Safety and tolerability

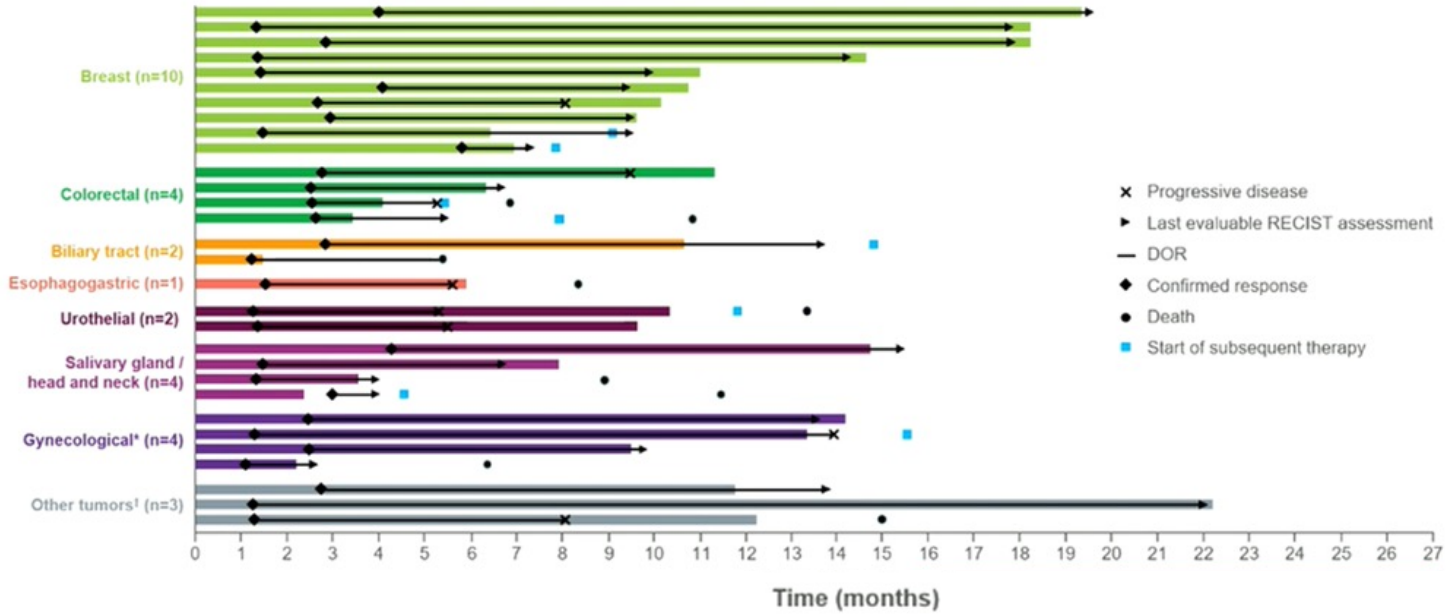


Li BT, et al. ESMO 2023. Abstract 654O

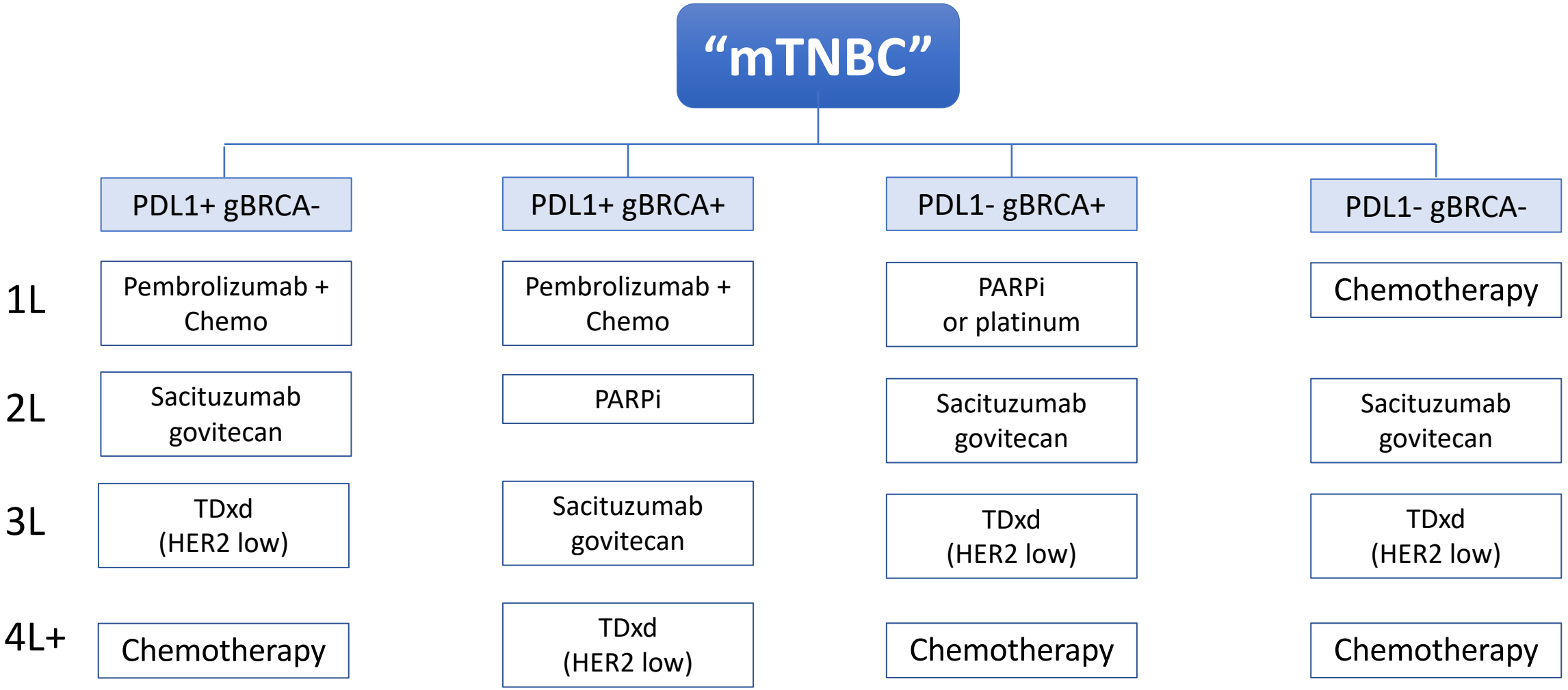
DESTINY-PanTumor01 (Phase 2): Efficacy – Best objective response (ICR) and duration of response (ICR)



Confirmed ORR by ICR 29.4% (95% CI 20.8, 39.3)



T-DXd, trastuzumab deruxtecan.
Li BT, et al. ESMO 2023. Abstract 654O



- Pembrolizumab 2L+ for solid tumors with **TMB-H (>10mut/Mb) or MSI-high**
- ***NTRK* fusion**: Larotrectinib or entrectinib for metastatic solid tumor

Adapted from NCCN 4.2023 & ESMO Guidelines

Phase III Ascent Trial: Sacituzumab Govitecan vs. TPC in TNBC

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

Metastatic TNBC (per ASCO/CAP)
≥2 chemotherapies for advanced disease
[no upper limit; 1 of the required prior regimens could be progression occurred within a 12-month period after completion of (neo)adjuvant therapy)]
N=529

R 1:1

- **Sacituzumab Govitecan (SG)** 10 mg/kg IV days 1 & 8, every 21-day cycle (n=267)
- **Treatment of Physician's Choice (TPC)*** (n=262)

Continue treatment until progression or unacceptable toxicity

Endpoints
Primary
- PFS†

Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

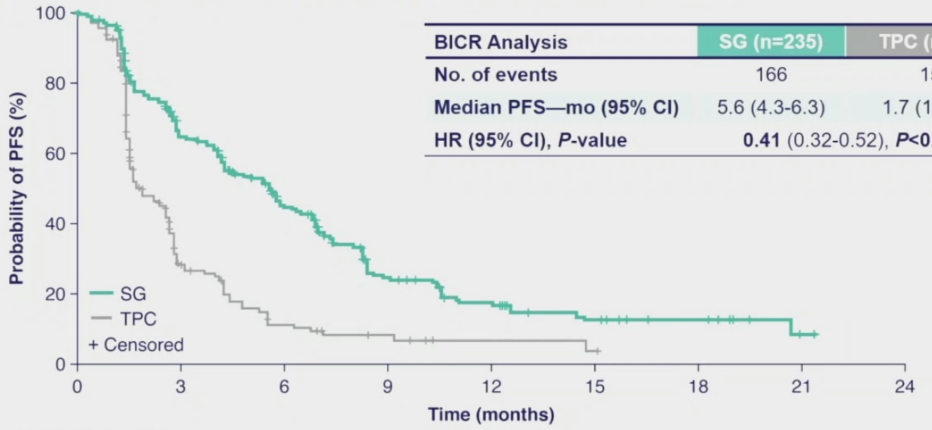
Data cutoff: March 11, 2020

NCT02574455

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

Progression-Free Survival (BICR Analysis)



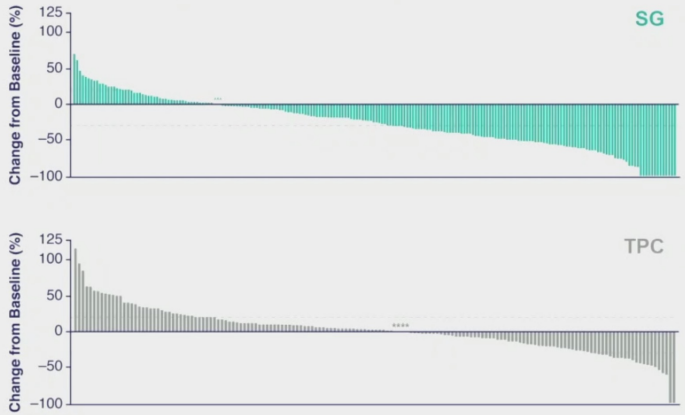
BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

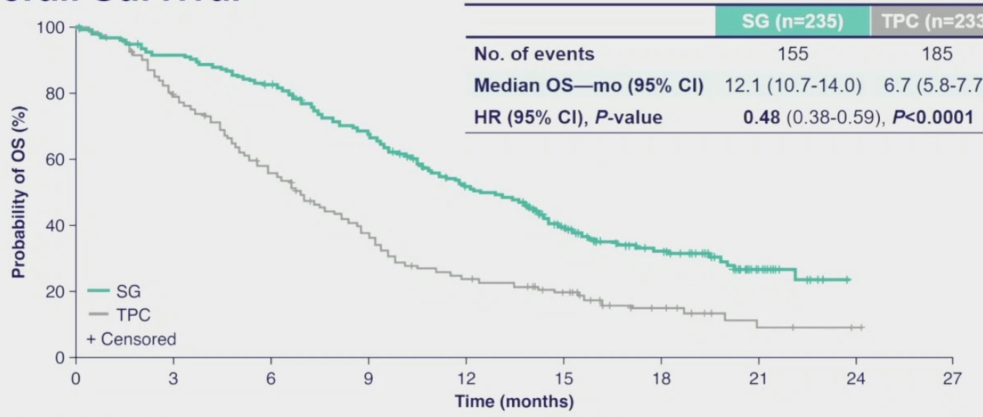
Overall Response and Best Percent Change From Baseline in Tumor Size



	SG (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	
Median DOR —mo (95%CI)	6.3 (5.5–9.0)	3.6 (2.8–NE)
P-value	0.057	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

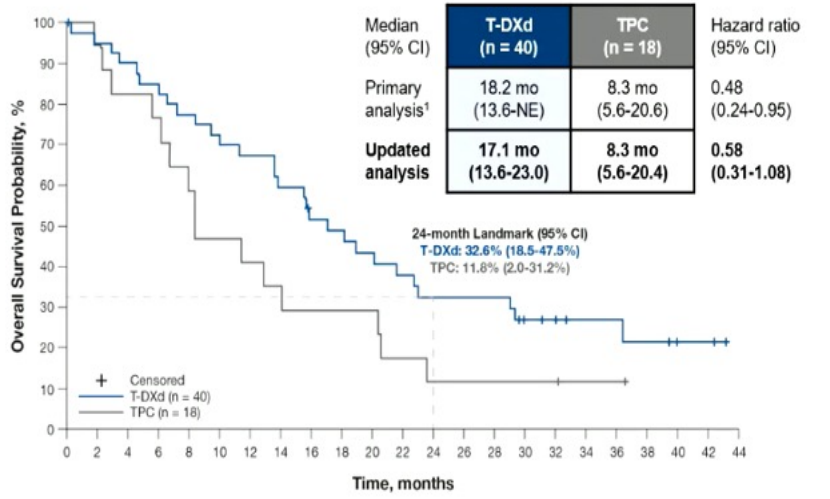
Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Bardia et al. NEJM 2021 (PMID: 30786188)

DESTINY-Breast04 (Phase 3, update): T-DXd v TPC among patients with HER2-low unresectable and/or metastatic breast cancer

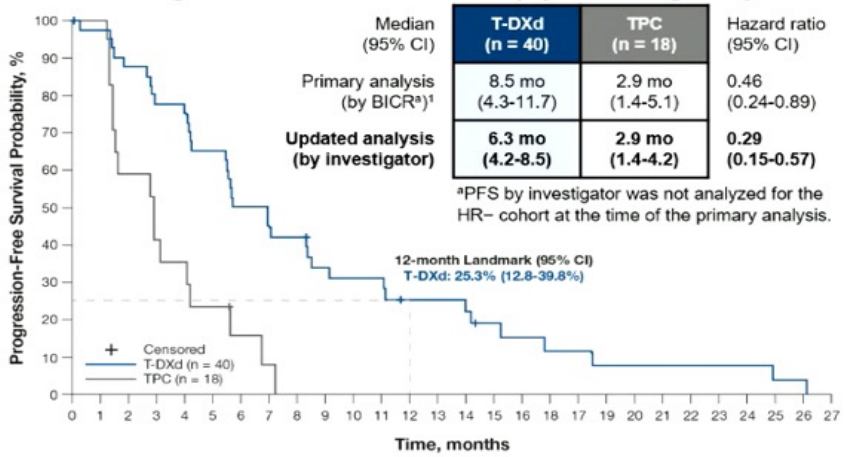
Efficacy in the HR− cohort (exploratory analyses)

Overall Survival



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

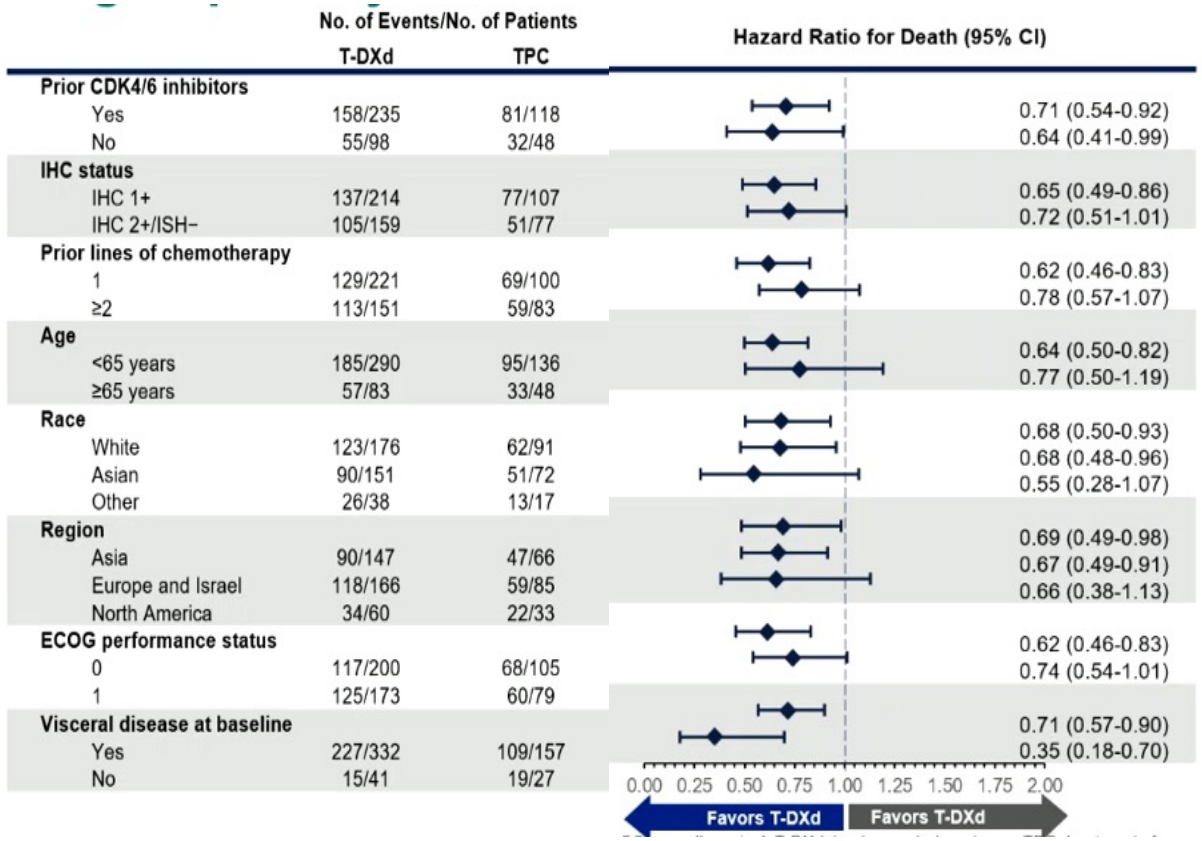
Progression-Free Survival (by Investigator)



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

Subgroup analyses



	No. of Events/No. of Patients		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	
Prior CDK4/6 inhibitors			
Yes	158/235	81/118	0.71 (0.54-0.92)
No	55/98	32/48	0.64 (0.41-0.99)
IHC status			
IHC 1+	137/214	77/107	0.65 (0.49-0.86)
IHC 2+/ISH−	105/159	51/77	0.72 (0.51-1.01)
Prior lines of chemotherapy			
1	129/221	69/100	0.62 (0.46-0.83)
≥2	113/151	59/83	0.78 (0.57-1.07)
Age			
<65 years	185/290	95/136	0.64 (0.50-0.82)
≥65 years	57/83	33/48	0.77 (0.50-1.19)
Race			
White	123/176	62/91	0.68 (0.50-0.93)
Asian	90/151	51/72	0.68 (0.48-0.96)
Other	26/38	13/17	0.55 (0.28-1.07)
Region			
Asia	90/147	47/66	0.69 (0.49-0.98)
Europe and Israel	118/166	59/85	0.67 (0.49-0.91)
North America	34/60	22/33	0.66 (0.38-1.13)
ECOG performance status			
0	117/200	68/105	0.62 (0.46-0.83)
1	125/173	60/79	0.74 (0.54-1.01)
Visceral disease at baseline			
Yes	227/332	109/157	0.71 (0.57-0.90)
No	15/41	19/27	0.35 (0.18-0.70)

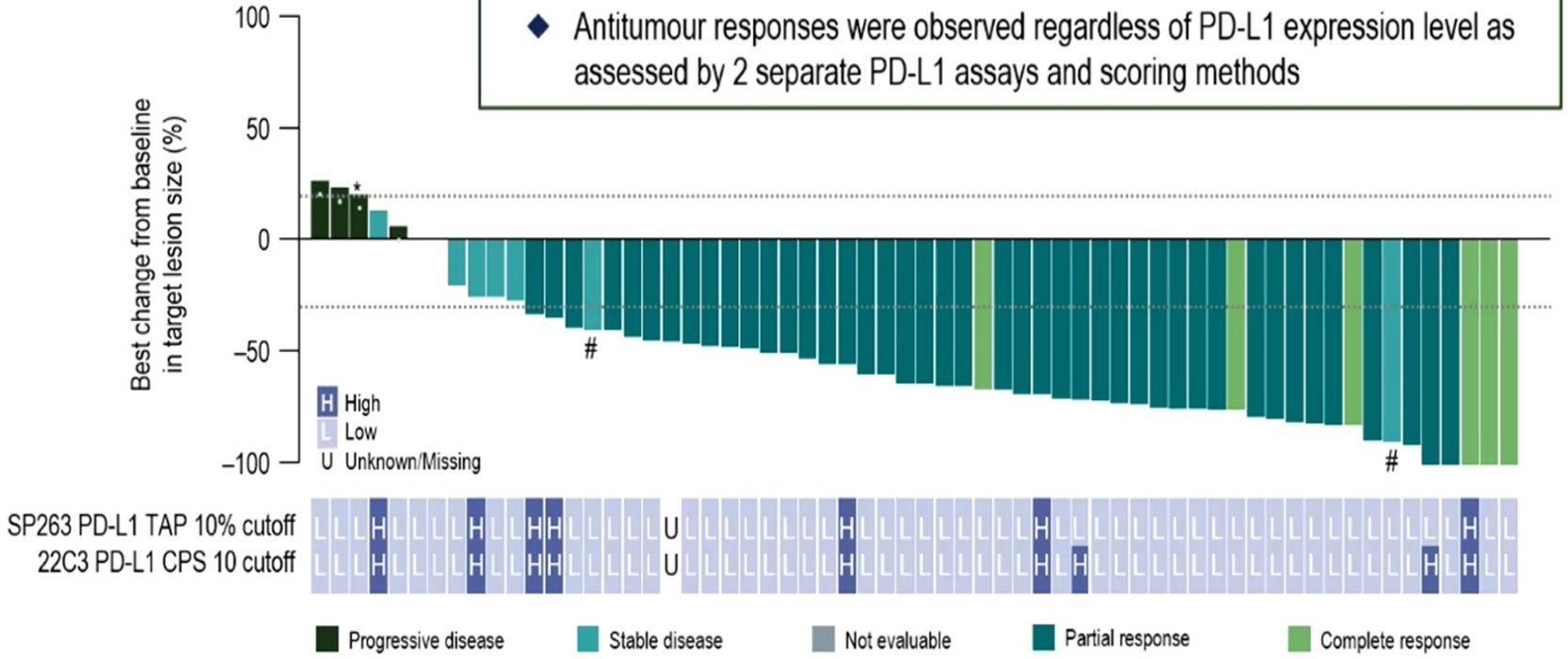
- 42% reduction in risk of death and 71% reduction in risk of progression or death for HR− patients receiving T-DXd compared with TPC

at the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI: 31.0, 32.8 months)
TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan. Modi S, et al. ESMO 2023. Abstract 376O

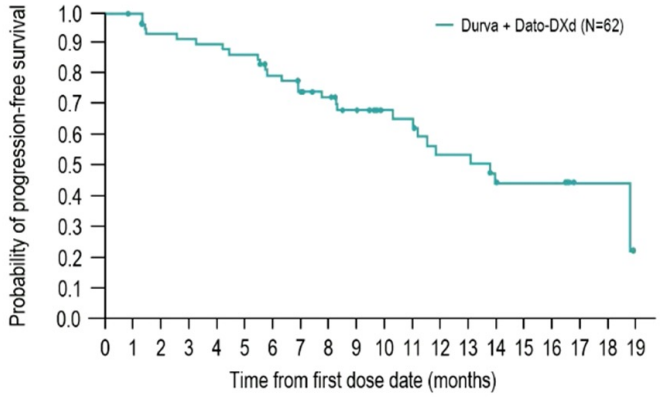
BEGONIA (Phase 1b/2): Anti-tumour efficacy in 1L /mTNBC with Datopotumab + Durvalumab every 3 weeks

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



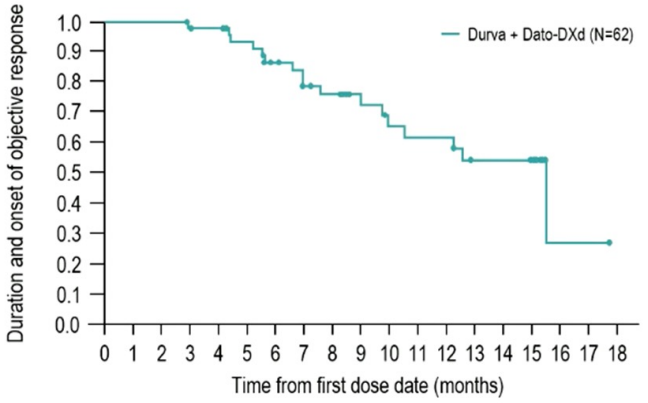
Median PFS was **13.8** months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was **15.5** months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Schmid P, et al. ESMO 2023. Abstract 379MO

BEGONIA (Phase 1b/2): Safety

Patients, n (%)	Dato-DXd + D N=62
Any AEs	62 (100)
Grade 3/4	35 (57)
Any treatment-related AEs[a]	62 (100)
Grade 3/4	27 (44)
Any serious AEs	14 (23)
Treatment-related	6 (10)
AEs leading to discontinuation of any treatments	10 (16)
AEs leading to death[b]	1 (2)
Dose adjustments	
Dato-DXd dose reduction	18 (29)
Dato-DXd dose delay	28 (45)
Durvalumab dose delay	31 (50)

Most frequently reported adverse events (≥15%) (N=62)

AE preferred term	Any grade, n (%)	Grade 3/4, n (%)
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

- The most common AEs were gastrointestinal and generally of low grade (**Table**)
- Stomatitis was the most common AE leading to Dato-DXd dose reduction (11 patients)
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade 2 events, 1 grade 1 event)
- Limited rates of diarrhea (13% any grade, 1 grade 3 event) and neutropenia (5% any grade, 1 grade 3 event) were reported
- The most frequent AESIs for Arm 7 were stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), and keratitis* (14.5%)

Schmid P, et al. ESMO 2023. Abstract 379MO

Continued Progress in MBC 2023

- 1L HR+ HER2- MBC – almost all pts benefit from ET + CDKi > chemotherapy
- Elacestrant benefits pts with ESR1 mutations and prior CDK4/6i > 12 mos
- Capivasertib + fulvestrant – new option for PIK3CA, AKT, PTEN- mutant HR+ HER2- MBC
- TDX-d effective against HER2+ untreated active brain metastasis
- TDX-d active in HER2 0 and HER2 low pts with activating HER2 mutation
- Datopotumab – anti-TROP2 ADC with deruxtecan payload – in phase III, superior PFS vs chemoRx physician choice in 2L/3L HR+ HER2- MBC
- 1L mTNBC Begonia trial – Durvalumab + Dato – promising activity PDL1+/-