NCCN 2023 BREAST CANCER CONGRESS
with Updates from the 2022 San Antonio Breast Cancer Symposium

Friday, February 3, 2023
3:10 PM – 4:25 PM [CST]

Advances in the Management of Metastatic Breast Cancer with SABCS Updates

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NCCN 2023 BREAST CANCER CONGRESS
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Advances in the Management of Metastatic Breast Cancer with SABCS Updates

HR-Positive, HER2-Negative Metastatic Breast Caner

Chau T. Dang, MD

Memorial Sloan Kettering Cancer Center

What do we do after progression on CDK 4/6i?

AI + CDK 4/6*i or*
FUL + CDK 4/6*i*

???

- Limited prospective data to guide treatment decisions following clinical progression on CDK 4/6 inhibitor
- *PIK3CA* and *ESR-1* mutations contribute to endocrine resistance.
- In current practice, sequential endocrine monotherapy or combination therapies are used in the 2nd/3rd line
- PARP inhibitors for g*BRCA1/2*mut

Case # 1: HR+ HER2 IHC 1+

- Patient is 55 y/o postmenopausal female w/ de novo metastatic breast ca (MBC) from left sided breast ca with mets to bones and liver. Biopsy of left breast revealed IDC ER 50% PR 10% HER2 IHC 1+. Biopsy of a liver lesion revealed same biology; NGS on liver met revealed no actionable mutation. Germline testing was (-). She feels well and is asymptomatic of her metastatic disease. What is your recommendation for systemic therapy?

  A) Fulvestrant + CDK 4/6 inhibitor

  B) Aromatase inhibitor + CDK 4/6 inhibitor

  C) Fulvestrant

  D) Aromatase inhibitor

  E) A or B

CDK4/6 inhibitor Phase III trials in HR+MBC

Trial	Population	Previous CT allowed	Experimental arm	Median PFS (months)	Median OS (months)
PALOMA-2 [1-2]	Postmenop 1° line	Yes	Letro/Palb vs Letro/Plac	24.8 vs 14.5 m HR 0.58 p < 0.001	53.9 vs 51.2 m HR 0.956 p= NS
PALOMA-3 [2-3]	Post and premenop 2° line	Yes	Fulv/Palb vs Fulv/Plac	9.2 vs 3.8 m HR 0.42 p < 0.001	34.9 vs 22.0 m HR 0.81 P= NS
MONALEESA-2 [4-5]	Postmenop 1° line	Yes	Letr/Ribo vs Letro/Plac	25.3 vs 16 HR 0.56 p= 9.63 x 10^{-8}	63.9 vs 54.1 m HR 0.76 p =0.008
MONALEESA-3 [6-7]	Postmenop 1° and 2°line	No	Fulv/Ribo vs Fulv/Plac	20.5 vs 12.8 m HR: 0.593 P < 0.001	NR vs 40.0 m HR 0.72 p= 0.0045
MONALEESA-7 [8-9]	Peri/Premenop 1° and 2°line	Yes	OS/ NSAI or Tam/Ribo vs OS/ NSAI or Tam/Plac	23.8 vs 13.0 m HR 0.55 P < 0.0001	NE vs 40.9 m HR 0.71 p= 0.00973
MONARCH-3 [10-11]	Postmenop 1° line	No	Letro/Abma vs Letro/Plac	28.2 vs 14.8 m HR 0.54 P=0000021	67.1 vs 54.5 m HR = 0.754 P=0.0301
MONARCH-2 [12-13]	Postmenop 1° and 2°line or later	No	Fulv/Abema vs Fulv/Plac	16.4 vs 9.3 HR 0.53 P < 001	46.7 vs 37.3 HR 0.75 p=0.01

1. Finn et al. NEJM 2016; 2. Finn et al. ASCO 2022; 3. Turner et al. NEJM 2015; 4. Turner et al. NEJM 2018; 4. Hortobagyi et al. Ann Onc 2019;
5. Hortobagyi et al. NEJM 2022; 6. Slamon et al. JCO 2018; 7. Slamon et al. NEJM 2020; 8. Tripathy et al. Lancet Onc 2018; 9. Im et al. NEJM 2019
10. Goetz et al. JCO 2017; 11. Goetz et al. ESMO 2022; 12. Sledge et al. JCO 2017; 13. Sledge et al. JAMA Onc 2020

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Breast Cancer

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
- Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Addtional targeted therapy options, see BINV-Q (6)

HER2-Positive and Postmenopausal[m,n] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

Case # 1: HR+ HER2 IHC 1+ (Continued)

- She did well on 1L treatment for about 2 years and then experienced progression of disease in her liver and bone lesions. She was then placed on capecitabine and partial response until about 6 months later, CT CAP showed progression in her liver. What is next best option?

  A) Paclitaxel

  B) Gemcitabine

  C) Fam-Trastuzumab deruxtecan

  D) Sacituzumab

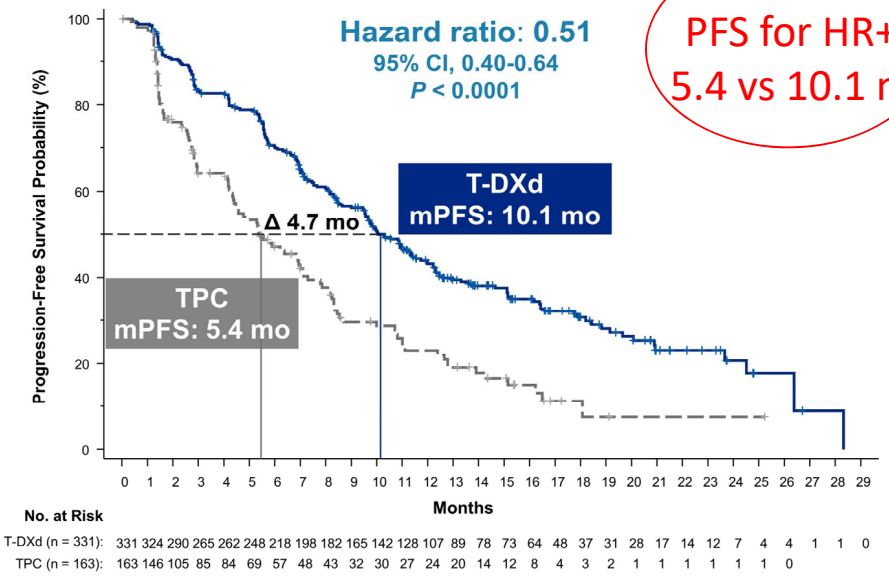
DESTINY Breast-04

HER2 Low
1-2 prior lines chemo in MBC
HR+ dz (endocrine refractory)

DESTINY-Breast04

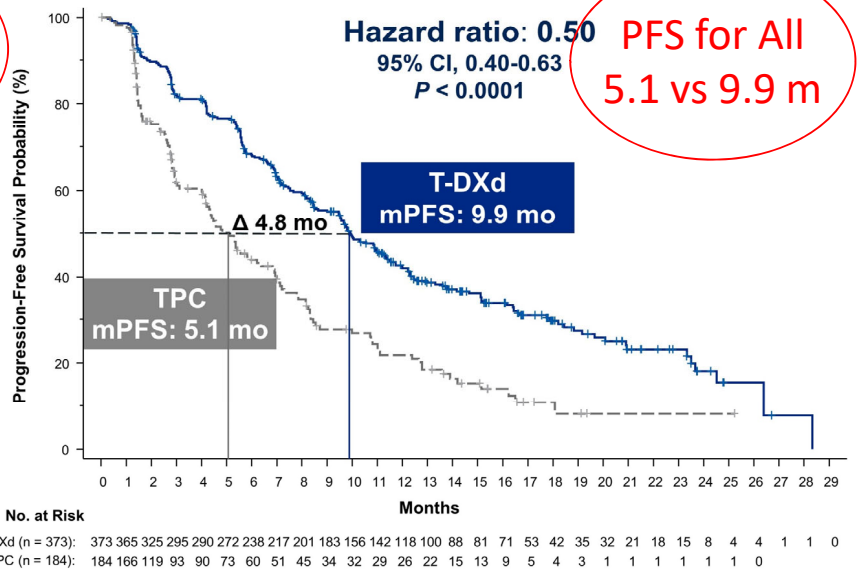
PFS in HR+ and All Patients

Hormone receptor–positive



PFS for HR+
5.4 vs 10.1 m

All patients



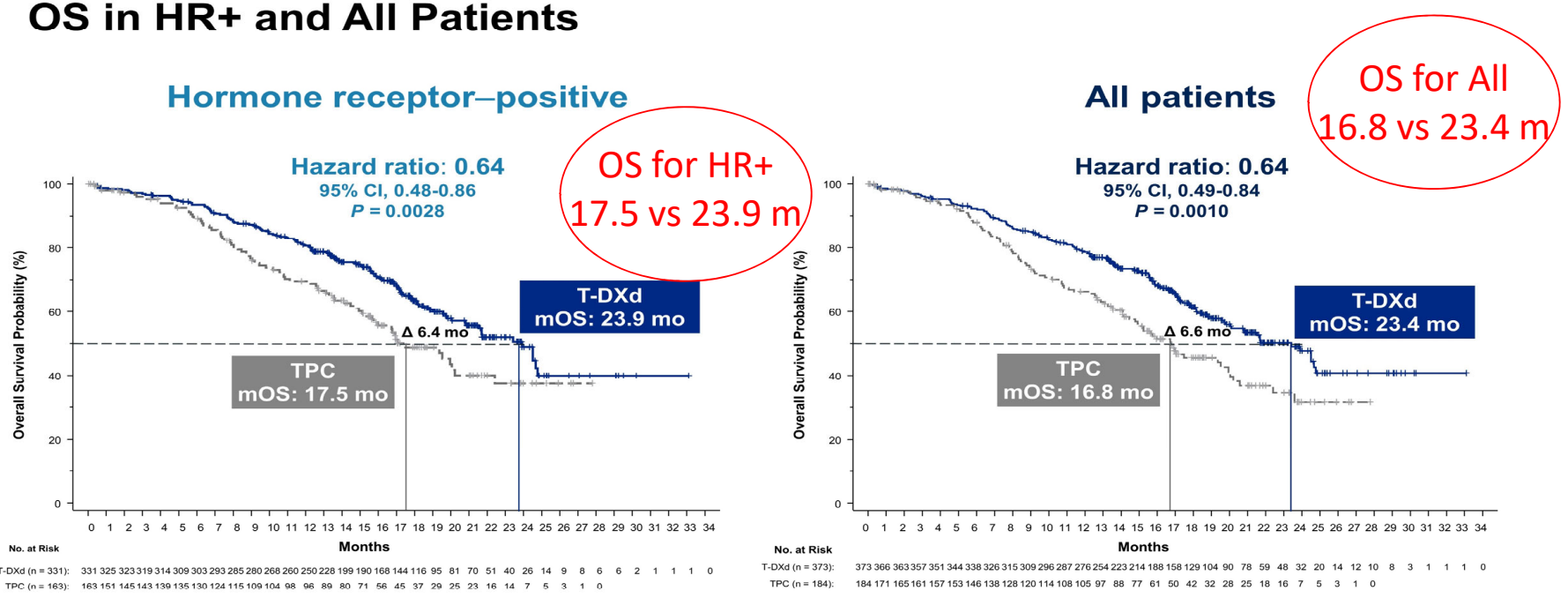
PFS for All
5.1 vs 9.9 m

PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

DESTINY Breast-04

DESTINY-Breast04

OS in HR+ and All Patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Shanu Modi, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

DESTINY-Breast04

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

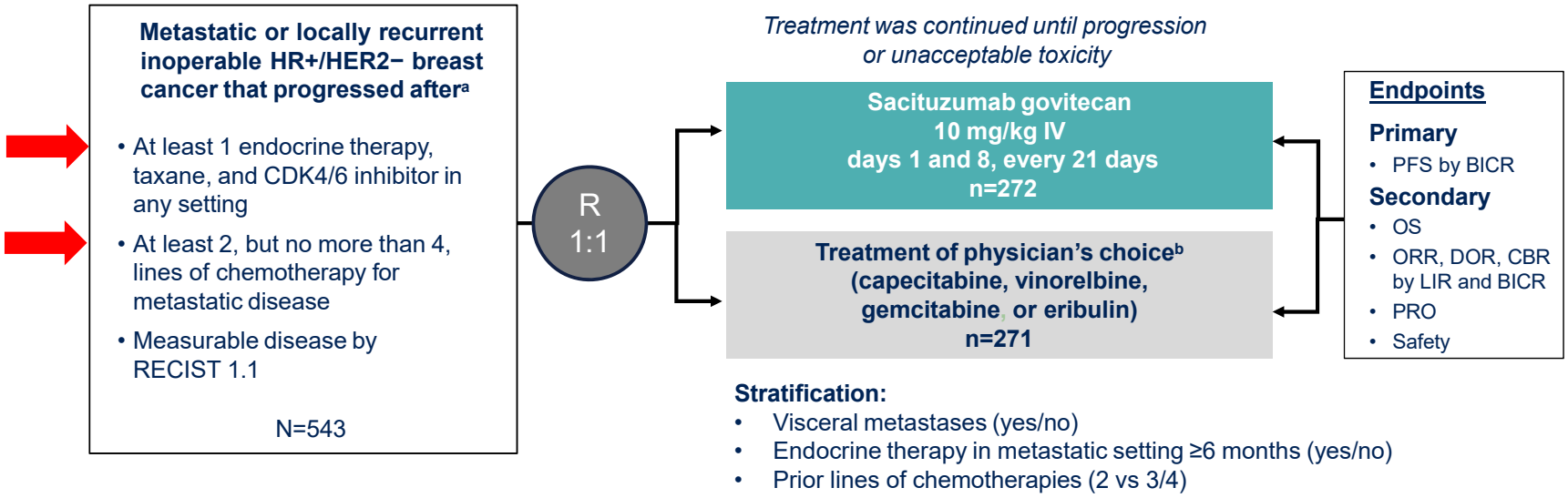
Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

PRESENTED BY:
Shanu Modi, MD

TROPiCS-02 (NCT03901339): A Phase 3 Study of SG in HR+/HER2– Locally Recurrent Inoperable or Metastatic Breast Cancer

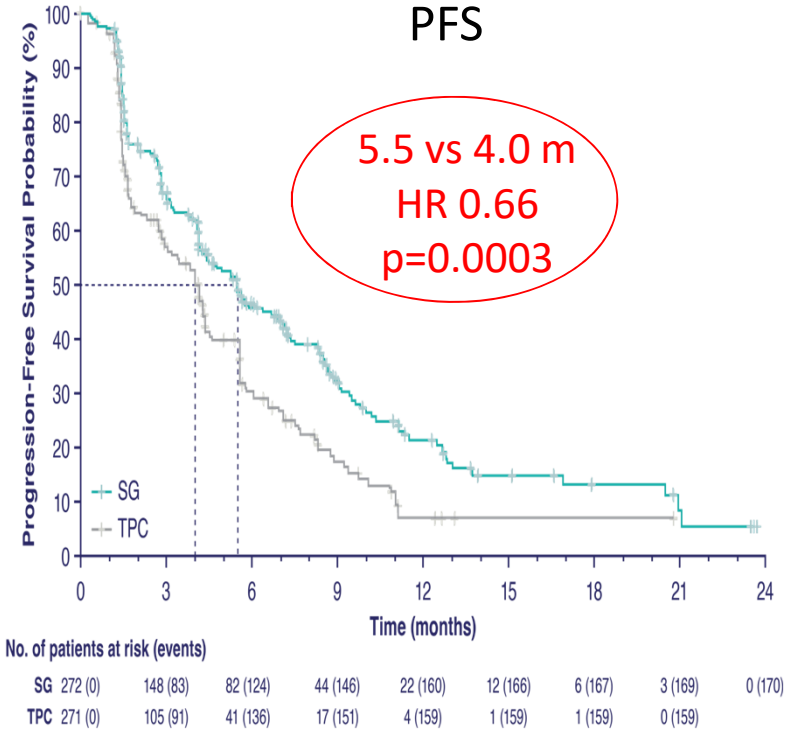


[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Presented by: Hope S. Rugo, MD
ESMO 2022

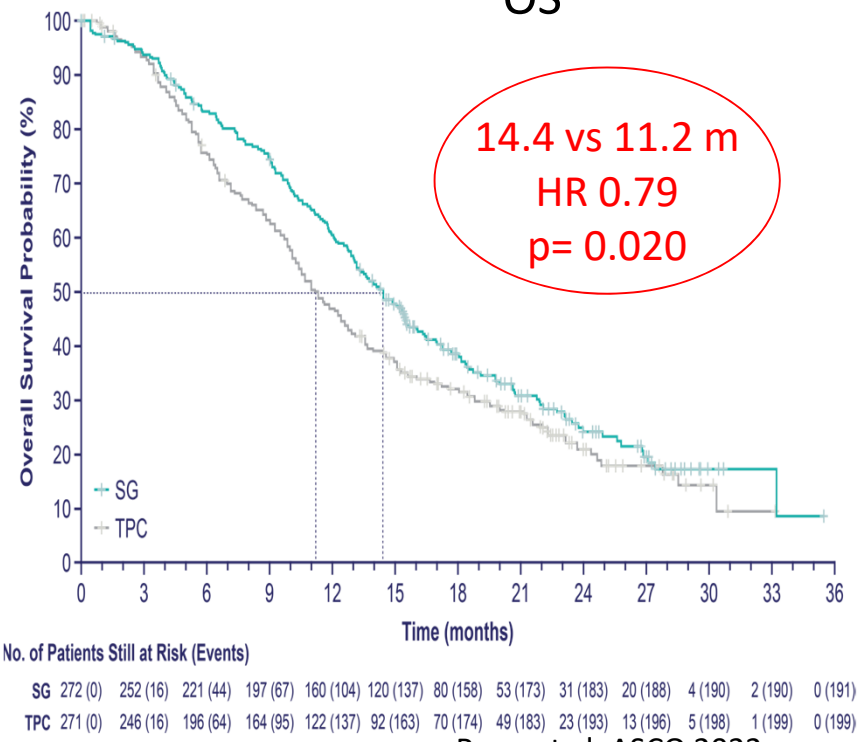
TROPiCS-02: PFS and OS

PFS



5.5 vs 4.0 m
HR 0.66
p=0.0003

OS



14.4 vs 11.2 m
HR 0.79
p= 0.020

Rugo et al. ASCO 2022
Rugo et al. ESMO 2022

Key All Grade and Grade ≥3 Treatment-Related Adverse Events[a]

TRAEs, n (%)		SG (n=268)		TPC (n=249)	
		All grade	Grade ≥3	All grade	Grade ≥3
Hematologic	**Neutropenia[b]**	188 (70)	**136 (51)**	134 (54)	**94 (38)**
	Anemia[c]	91 (34)	17 (6)	62 (25)	8 (3)
	Leukopenia[d]	37 (14)	23 (9)	23 (9)	13 (5)
	Lymphopenia[e]	31 (12)	10 (4)	25 (10)	8 (3)
	Febrile neutropenia	**14 (5)**	**14 (5)**	**11 (4)**	**11 (4)**
Gastrointestinal	**Diarrhea**	152 (57)	**25 (9)**	41 (16)	**3 (1)**
	Nausea	148 (55)	3 (1)	77 (31)	7 (3)
	Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
	Constipation	49 (18)	0	36 (14)	0
	Abdominal pain	34 (13)	2 (1)	17 (7)	0
Other	Alopecia	123 (46)	0	41 (16)	0
	Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
	Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
	Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
	Neuropathy[f]	23 (9)	3 (1)	38 (15)	6 (2)

- **There were no events of interstitial lung disease in the SG arm (vs 1% in the TPC arm) and no TRAEs of cardiac failure or left ventricular dysfunction in either arm**

Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than one event per preferred term.
[a]Key All Grade and Grade ≥3 TRAEs defined as those occurring in ≥10% and ≥5% of patients in one arm, respectively. [b]Combined preferred terms of 'neutropenia' and 'neutrophil count decreased.' [c]Combined preferred terms of 'anemia,' 'hemoglobin decreased,' and 'red blood cell count decreased.' [d]Combined preferred terms of 'leukopenia' and 'white blood cell count decreased.' [e]Combined preferred terms of 'lymphopenia' and 'lymphocyte count decreased'. [f]Combined preferred terms of 'gait disturbance', 'hypoesthesia', 'muscular weakness', 'neuropathy peripheral', 'paraesthesia', and 'peripheral sensory neuropathy';
SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related adverse event.

FDA Approves Sacituzumab Govitecan for Pretreated HR+/HER2– Metastatic Breast Cancer

Feb 3, 2023

The FDA has approved sacituzumab govitecan-hziy for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor–positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.

The FDA has approved sacituzumab govitecan-hziy for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor–positive, HER2-negative breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting.[1]

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NCCN Guidelines Version 1.2023
Breast Cancer

NCCN Guidelines Index
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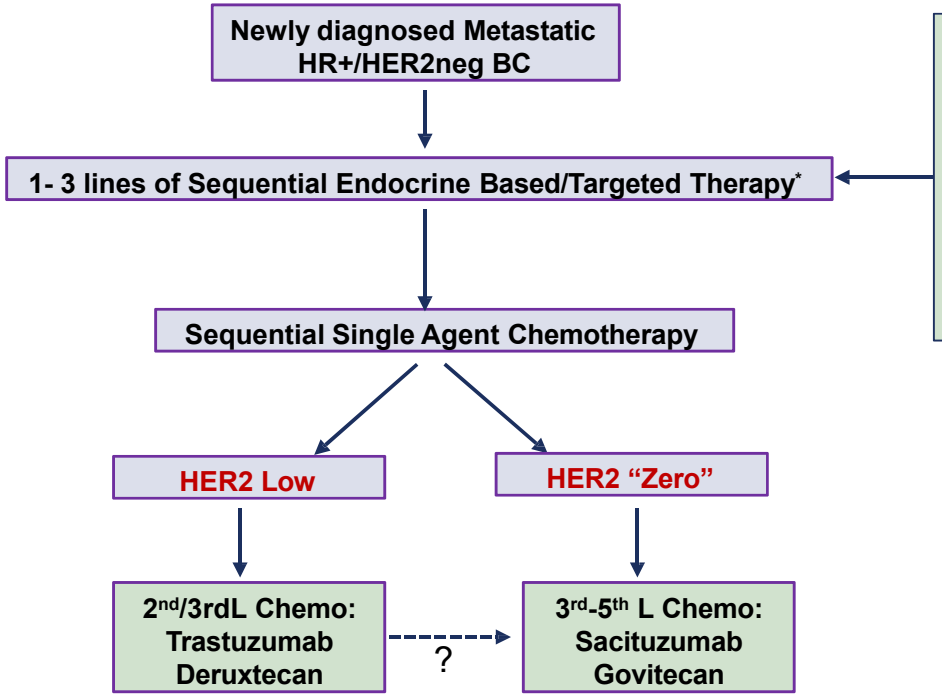
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

Treatment Roadmap for HR+/HER2- MBC Today in Clinic



1st L: - AI/SERD + CDK4/6i

2nd or 3rd L: - SERD + PI3Ki (*PIK3CA mutant*)
- ET + mTORi
- SERD + CDK4/6i

1-3rd L: - *gBRCA1/2+: PARPi*

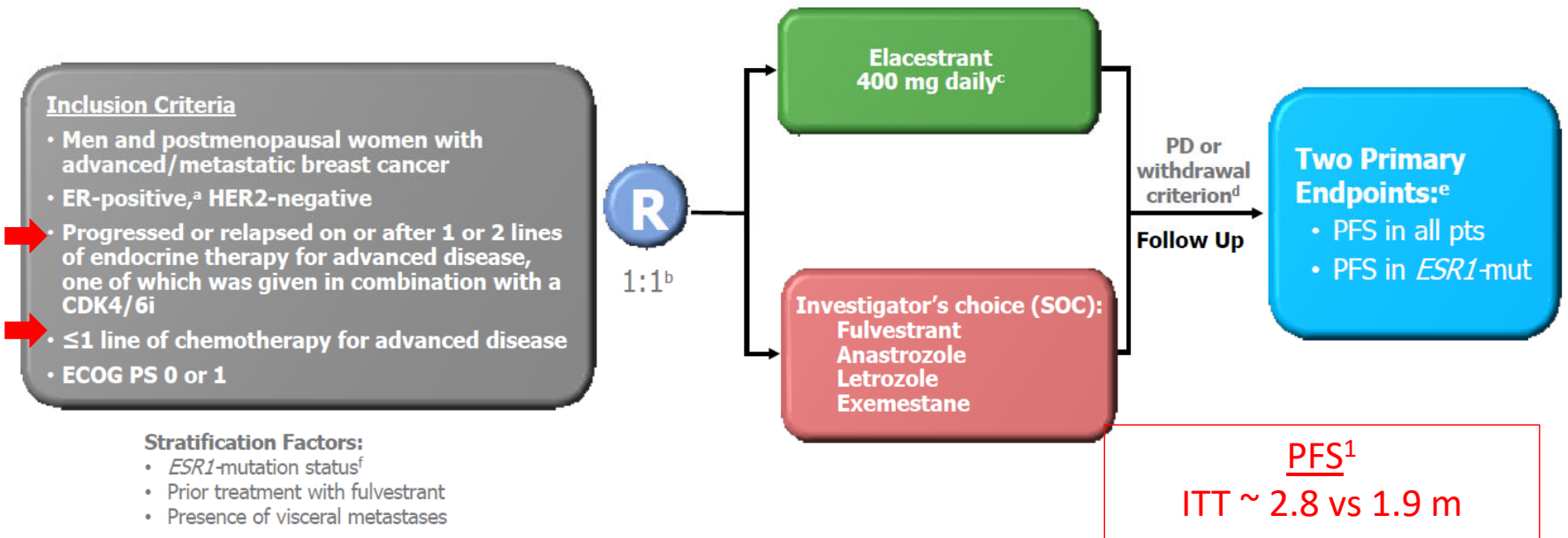
≥2nd L: - *Larotrectinib/Entrectinib (NTRK fusion)*
- *Pembrolizumab (MSI-H/dMMR, High TMB)*

*Chemotherapy for visceral crisis

Courtesy of Dr. Komal Jhaveri, MD FACP

SABCS 2022 Updates

EMERALD Phase 3 Study Design



PFS[1]
ITT ~ 2.8 vs 1.9 m
ESR1 mut+ ~ 3.8 vs 1.9 m

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

1. Bardia et al. JCO 2022
2. Bardia et al. SABCS 2022; GS03-01

Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	 233 (97.5) 6 (2.5)	 115 (100) 0	 238 (99.6) 1 (0.4)	 113 (100) 0
ECOG PS, n (%) 0 1 >1	 143 (59.8) 96 (40.2) 0	 67 (58.3) 48 (41.7) 0	 135 (56.5) 103 (43.1) 1 (0.4)	 62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	 129 (54.0) 110 (46.0)	 73 (63.5) 42 (36.5)	 142 (59.4) 97 (40.6)	 69 (61.1) 44 (38.9)
Type of prior endocrine therapy,** n (%) Fulvestrant AI Tamoxifen	 70 (29.3) 193 (80.8) 19 (7.9)	 27 (23.5) 101 (87.8) 9 (7.8)	 75 (31.4) 194 (81.2) 15 (6.3)	 28 (24.8) 96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	 191 (79.9) 48 (20.1)	 89 (77.4) 26 (22.6)	 180 (75.3) 59 (24.7)	 81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

Bardia et al. SABCS 2022; GS03-01

All Patients: PFS by Duration of CDK4/6i

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (87.5%)		At Least 12 Months (66.7%)		At Least 18 Months (46.7%)	
	Elacestrant (n=202)	SOC Hormonal Therapy (n=205)	Elacestrant (n=150)	SOC Hormonal Therapy (n=160)	Elacestrant (n=98)	SOC Hormonal Therapy (n=119)
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months, % (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months, % (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

Bardia et al. SABCS 2022; GS03-01

Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (92.3%)		At Least 12 Months (71.6%)		At Least 18 Months (50.0%)	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)	Elacestrant (n=55)	SOC Hormonal Therapy (n=56)
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months, % (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months, % (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Bardia et al. SABCS 2022; GS03-01

Safety Summary

Updated safety data were consistent with previously reported results:

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Bardia et al. SABCS 2022; GS03-01

FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

"On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy".

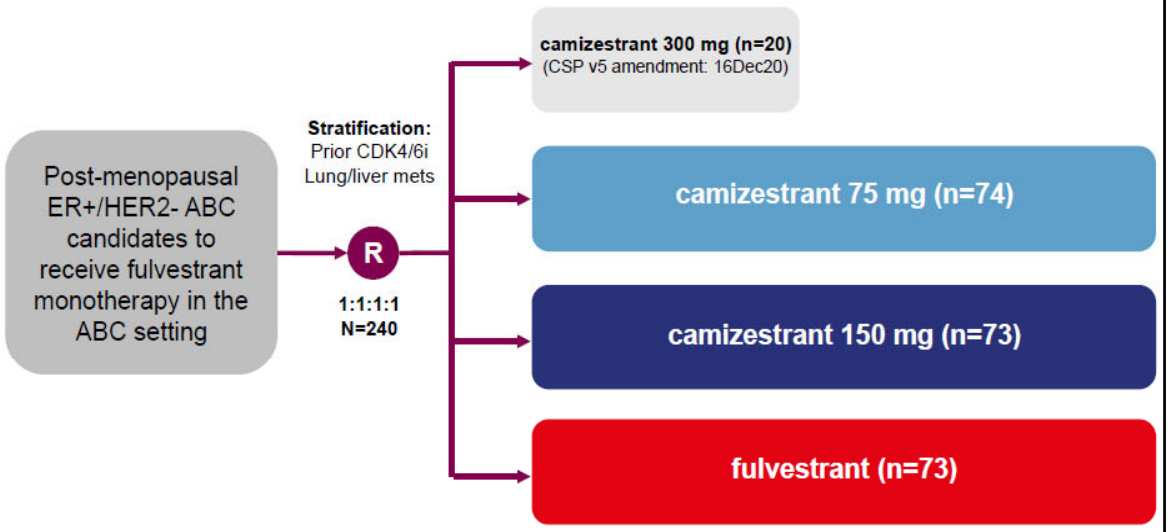
www.fda.org

SERENA-2 study overview

Key inclusion/exclusion criteria:

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease

50% had prior CDK 4/6 inh

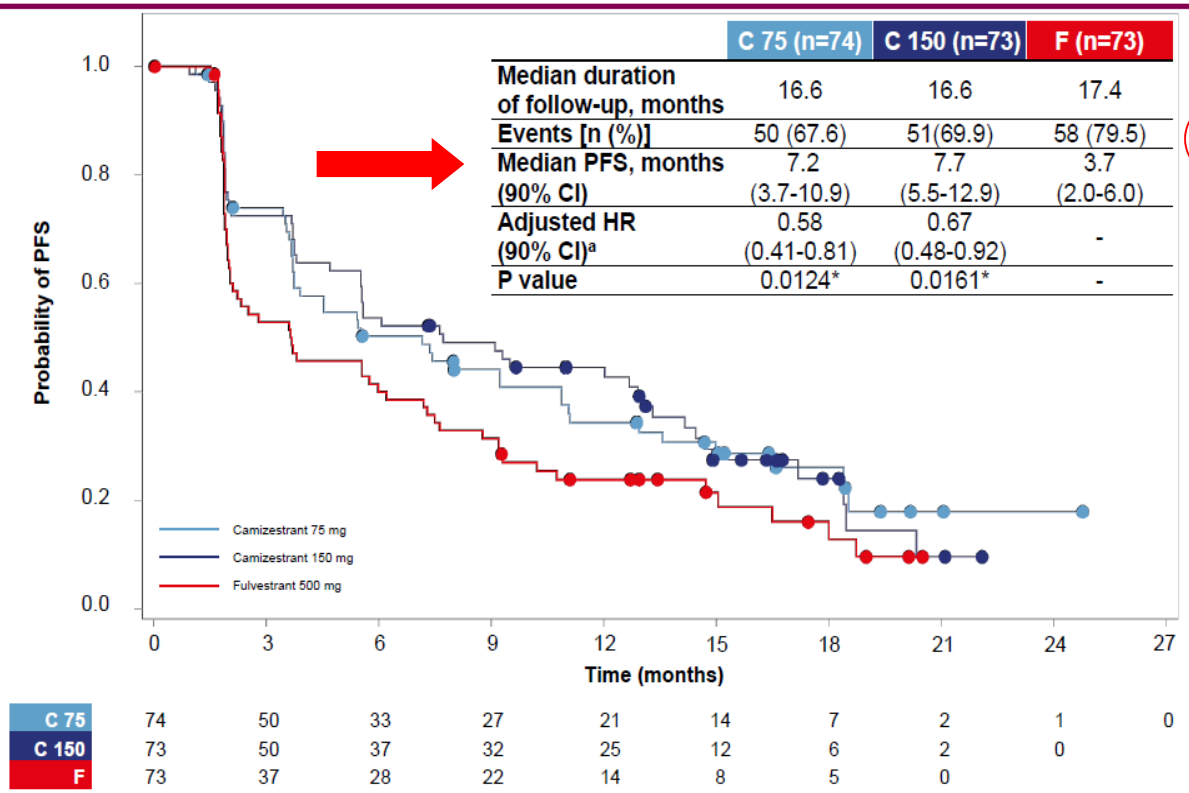


- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

*disease progression assessed by the Investigator and defined using RECIST, version 1.1
ABC: advanced breast cancer; CBR24: clinical benefit rate at 24 weeks; CDK4/6i: CDK4/6 inhibitor; CT: chemotherapy; CTC: circulating tumor cells; ctDNA: circulating tumor DNA; ER: estrogen receptor; *ESR1*m: mutation in estrogen receptor 1 gene; ET: endocrine therapy; HER2: human epidermal growth factor; PFS: progression-free survival; R: randomization; RECIST: Response Evaluation Criteria for Solid Tumors; SERD: selective estrogen receptor degrader

Oliveira et al. SABCS 2022; GS03-02

Primary endpoint: PFS by investigator assessment



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

C 75	74	50	33	27	21	14	7	2	1	0
C 150	73	50	37	32	25	12	6	2	0	
F	73	37	28	22	14	8	5	0		

*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

PFS
7.2 vs 7.7 vs 3.7 m

In the overall population, camizestrant produces a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

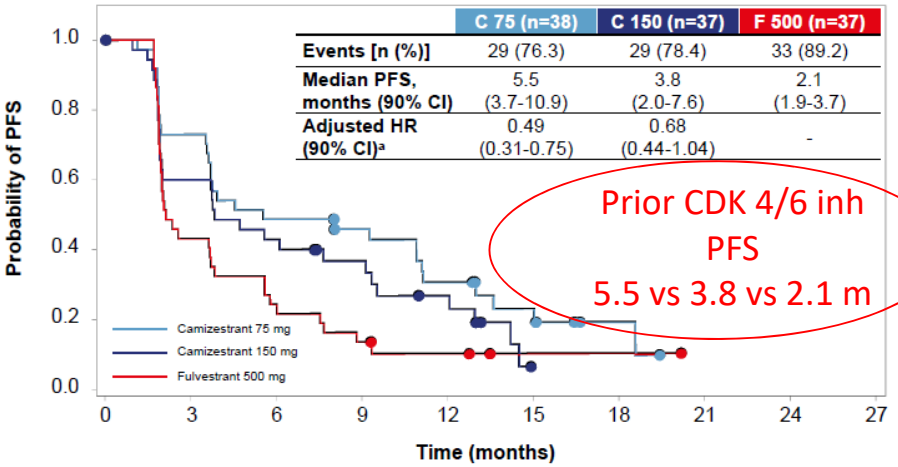
Oliveira et al. SABCS 2022; GS03-02

PFS in patients by prior use of CDK4/6i

No Prior CDK 4/6 inh
PFS
7.2 vs 14.7 vs 9.2 m

Prior CDK4/6i

	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

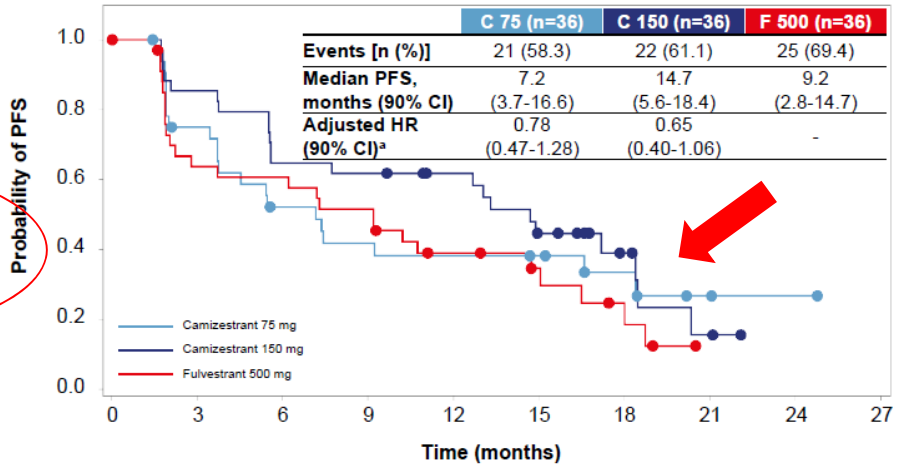


Prior CDK 4/6 inh
PFS
5.5 vs 3.8 vs 2.1 m

C 75	38	27	18	15	10	5	2	0
C 150	37	21	15	11	7	0		
F	37	16	8	5	3	1	1	0

No prior CDK4/6i

	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-



C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

- In the sub-population of patients previously treated with CDK4/6i + endocrine therapy, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

[a]HRs adjusted for liver/lung metastases

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; HR: hazard ratio; PFS: progression-free survival

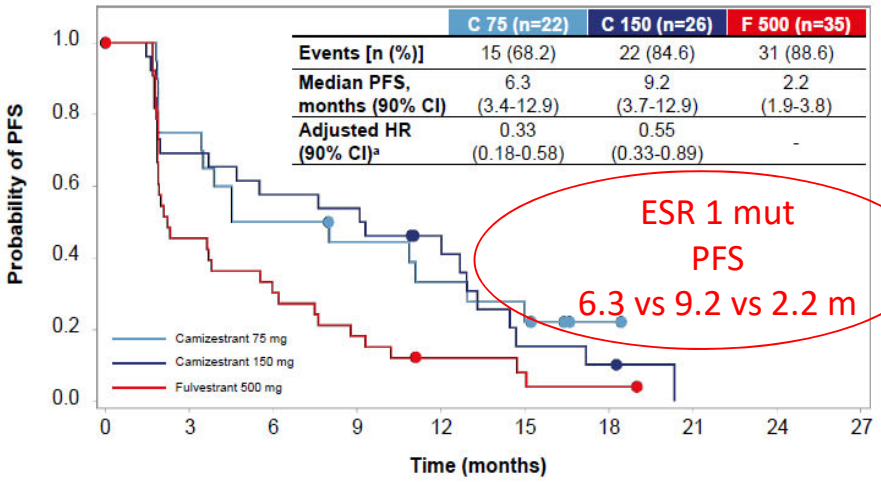
Oliveira et al. SABCS 2022; GS03-02

PFS in patients by detectable *ESR1*m

ESR 1 WT
PFS
7.2 vs 5.8 vs 7.2 m

*ESR1*m detectable at baseline

	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

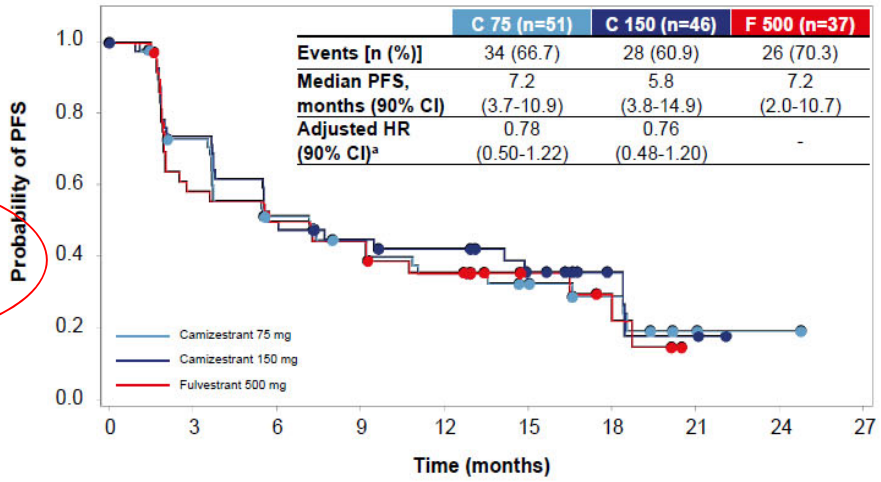


ESR 1 mut
PFS
6.3 vs 9.2 vs 2.2 m

C 75	22	15	10	8	6	4	1	0	
C 150	26	18	15	14	9	3	2	0	
F	35	15	10	6	3	2	1	0	

*ESR1*m not detectable at baseline

	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-



C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

- In the sub-population of patients with detectable *ESR1*m at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

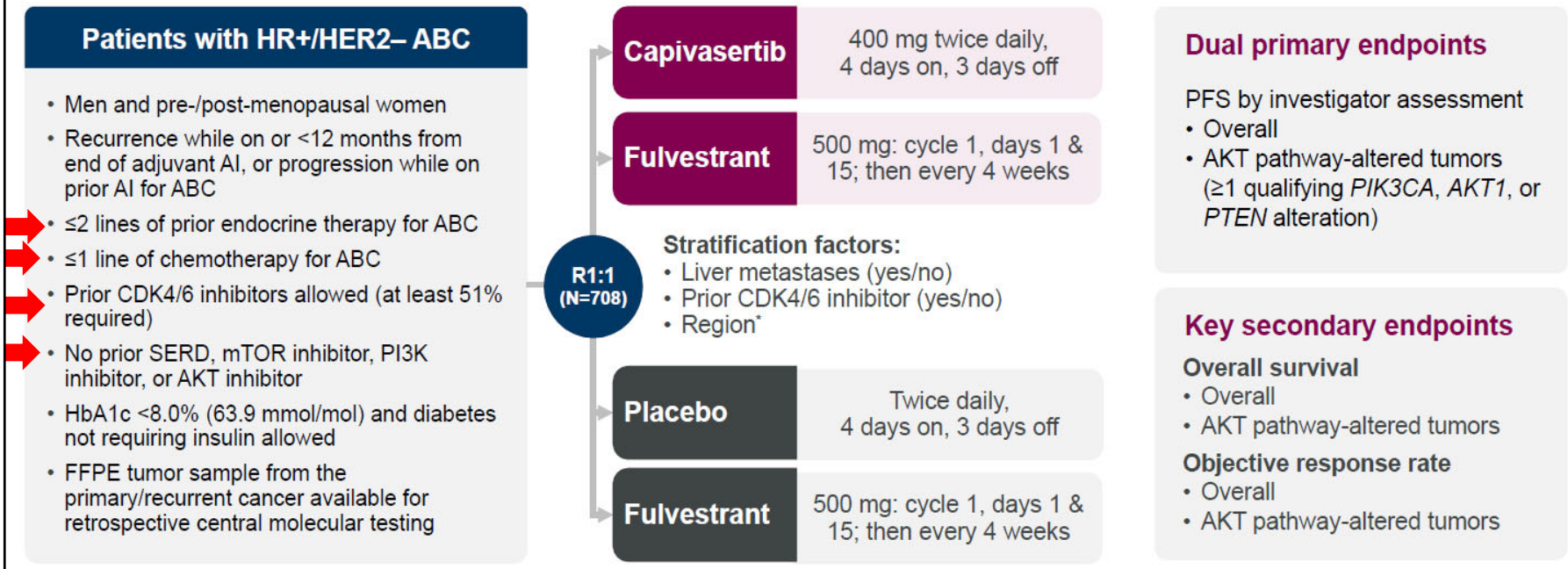
[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; ESR1m: mutation in estrogen receptor 1 gene; HR: hazard ratio; PFS: progression-free survival

Oliveira et al. SABCS 2022; GS03-02

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)



HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

Turner et al. SABCS; GS03-04

Baseline and tumor characteristics

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Median age; years (range)		59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female; n (%)		352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
Post menopausal; n (%)		287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
Race; n (%)	White	201 (56.6)	206 (58.4)	75 (48.4)	76 (56.7)
	Asian	95 (26.8)	94 (26.6)	48 (31.0)	35 (26.1)
	Black or African American	4 (1.1)	4 (1.1)	2 (1.3)	1 (0.7)
	Other	55 (15.5)	49 (13.9)	30 (19.4)	22 (16.4)
Region*; n (%)	1	197 (55.5)	198 (56.1)	80 (51.6)	76 (56.7)
	2	68 (19.2)	68 (19.3)	29 (18.7)	24 (17.9)
	3	90 (25.4)	87 (24.6)	46 (29.7)	34 (25.4)
Metastatic sites; n (%)	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver*	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
Hormone receptor status; n (%)†	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR-	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	ER+/PR unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance; n (%)	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)

*Baseline stratification factors. †One patient in the capivasertib + fulvestrant group was ER negative. Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia, Region 3: Asia. Primary and secondary resistance were defined using the 4th ESO-ESMO International Consensus Guidelines for ABC.

Turner et al. SABCS; GS03-04

Prior treatments

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

Turner et al. SABCS; GS03-04

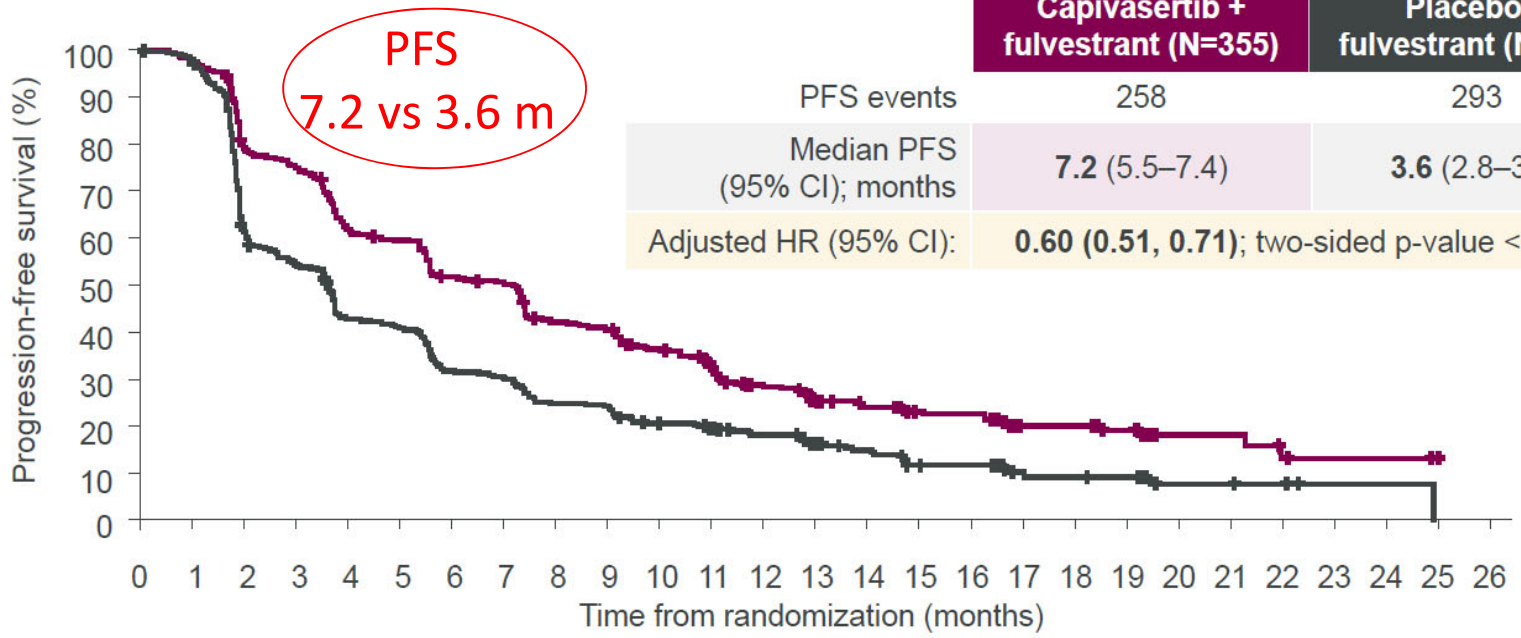
AKT pathway alterations

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Turner et al. SABCS; GS03-04

Dual-primary endpoint: Investigator-assessed PFS in the overall 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	

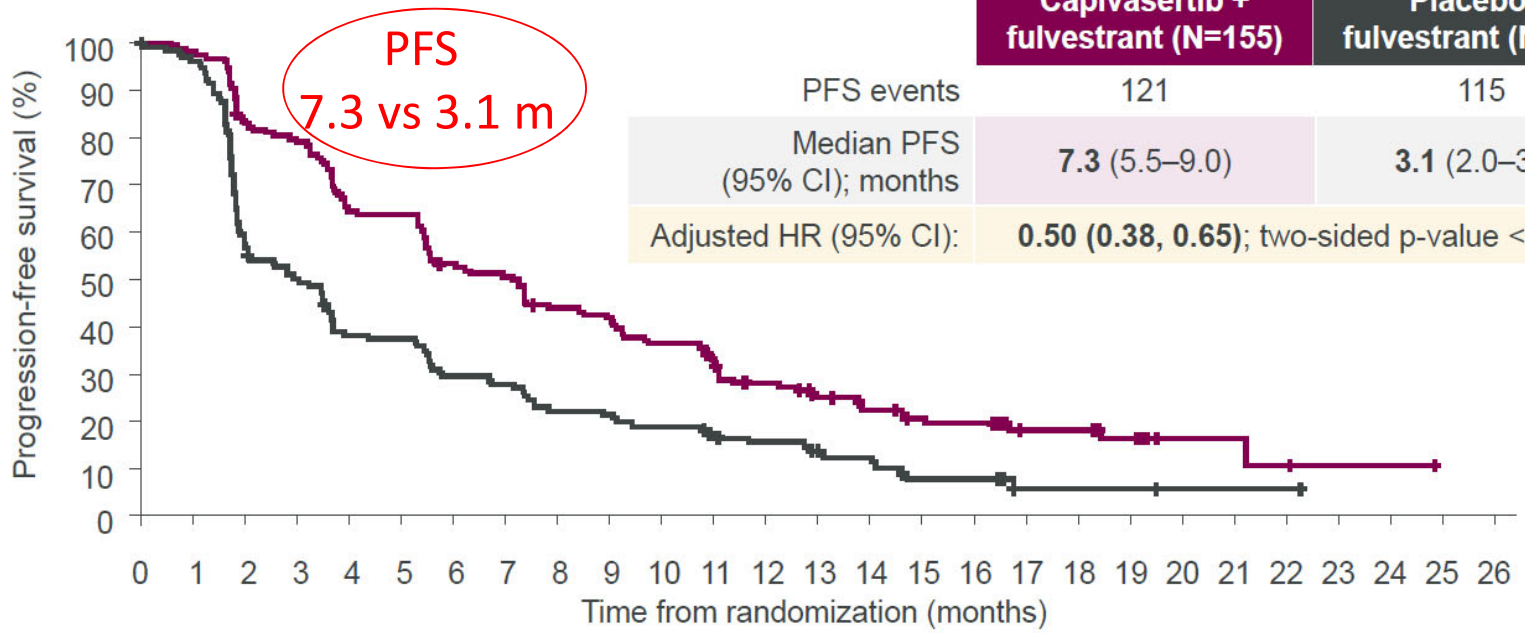
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Turner et al. SABCS; GS03-04

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered 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	

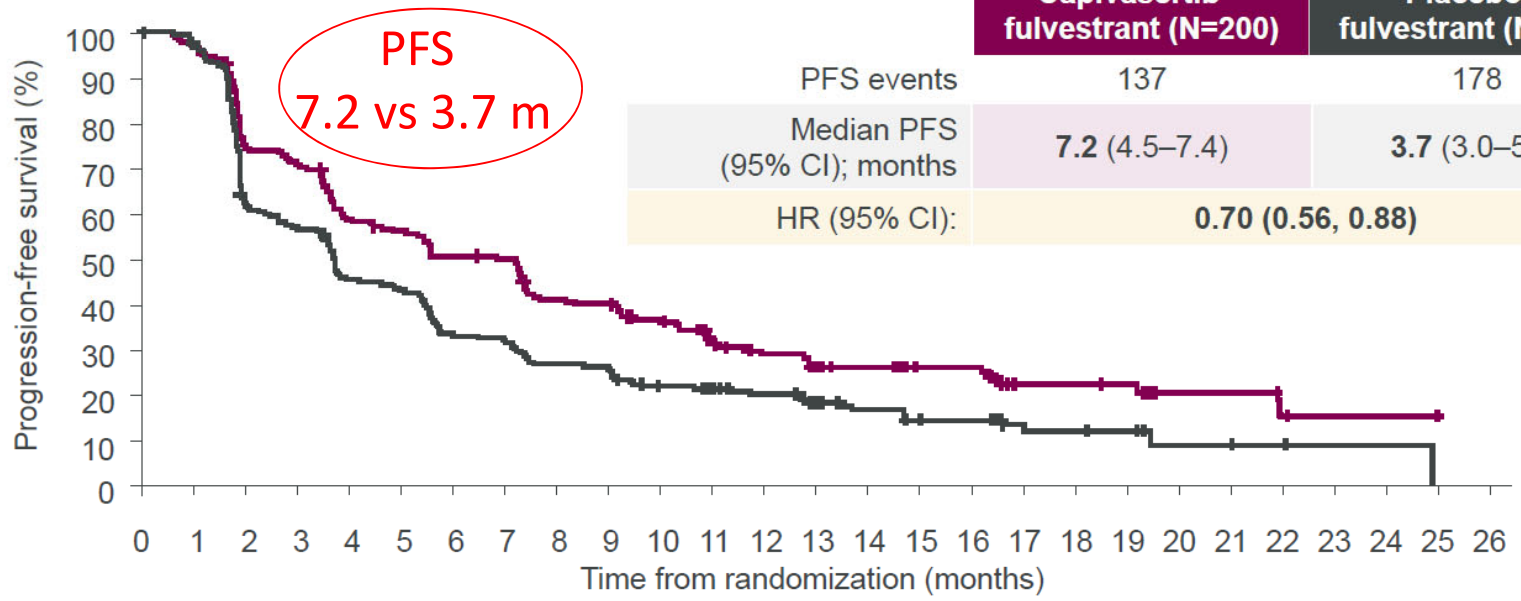
Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Turner et al. SABCS; GS03-04

Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)



	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	

Number of patients at risk

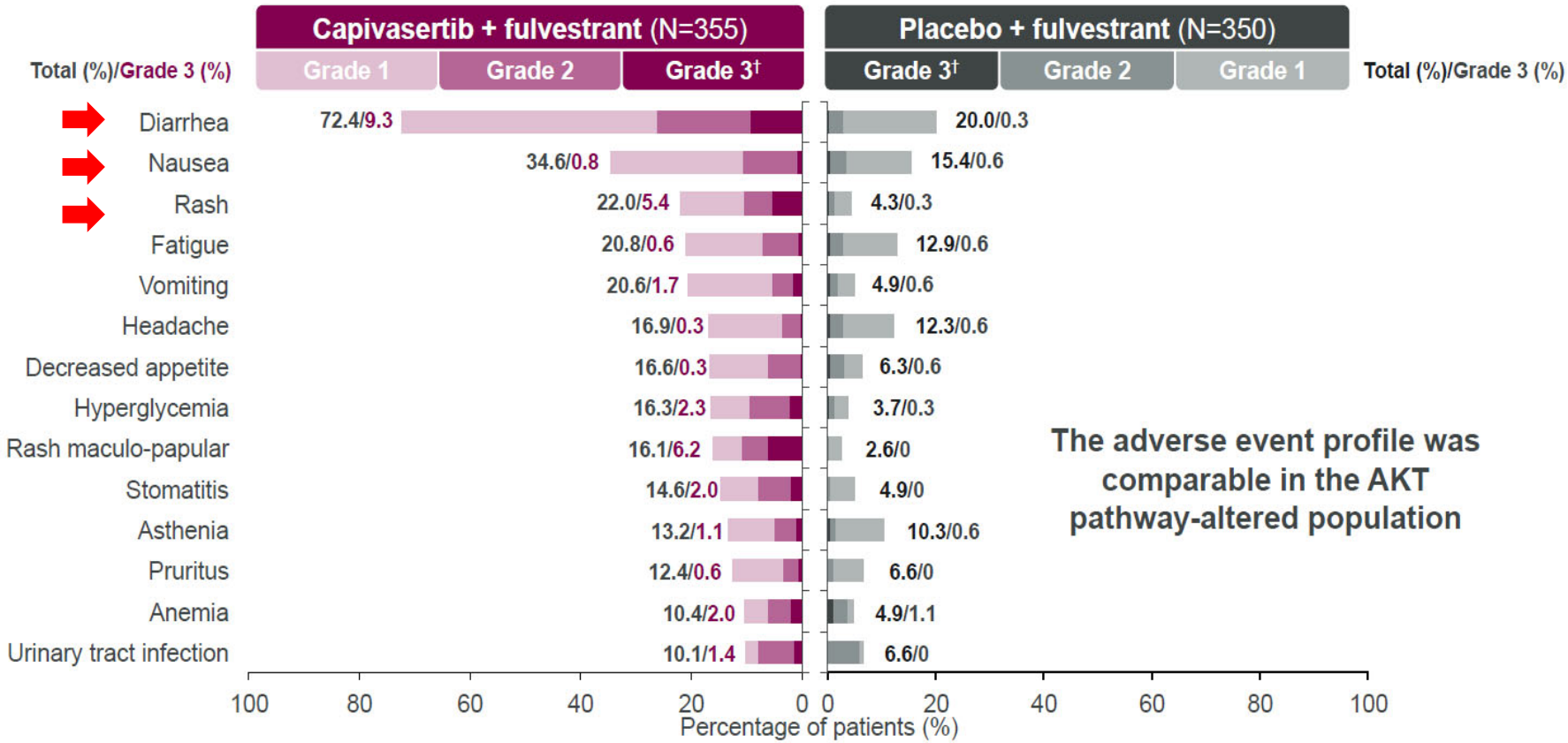
Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

+ indicates a censored observation. †Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Excluding unknowns:
HR 0.79 (95% CI 0.61, 1.02)

Turner et al. SABCS; GS03-04

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

Turner et al. SABCS; GS03-04

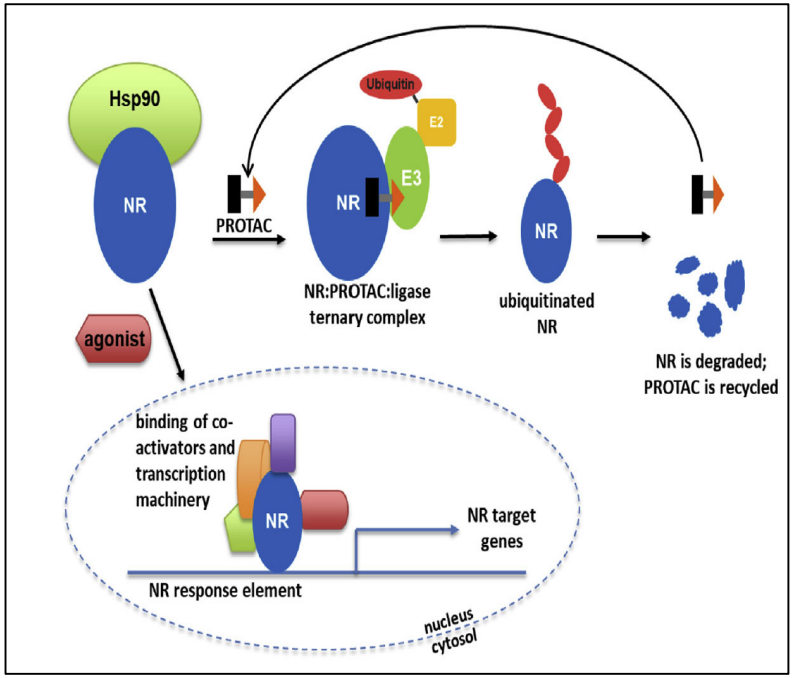
Summary

- Capivasertib + Fulvestrant ↑ PFS over Fulvestrant + Placebo in all and AKT pathway altered pts
- Safety Profile as expected
- This combination has potential to become another SOC after POD on prior endocrine-based Rx

VERITAC

ARV 471

- Phase 1 trial expansion cohort (Hurvitz et al SABCS 2022)
- N=71;
- Median 3 prior Rx in met setting
- 100% prior CDK4.5i, 79% prior fulvestrant and 45% prior chemo
- CBR: 38%; 51% in *ESR1m* (2 cPR)
- mPFS: 3.5m; 5.5m in *ESR1m* (n=41)
- Grade 1/2 nausea, fatigue, arthralgia, hot flush, AST increase
- Median ER degradation was 69%
- (range: 28%–95%)



Hurvitz et al. SABCS 2022; GS03-03

Option: CDK4/6*i* after CDK 4/6*i* – Pace Trial (Ph II)

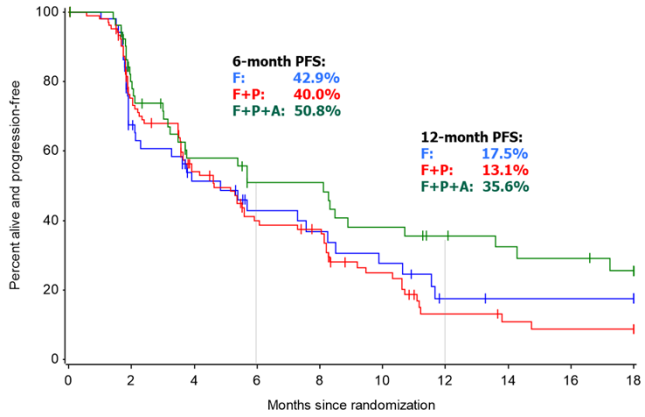
Aim: (1) Role of maintaining CDK4/6i beyond progression, with change of ET to fulvestrant, (2) adding ICPi

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

N=220

RANDOMIZE

- **Fulvestrant**
- **Fulvestrant + Palbociclib**
- **Fulvestrant + Palbociclib + Avelumab**



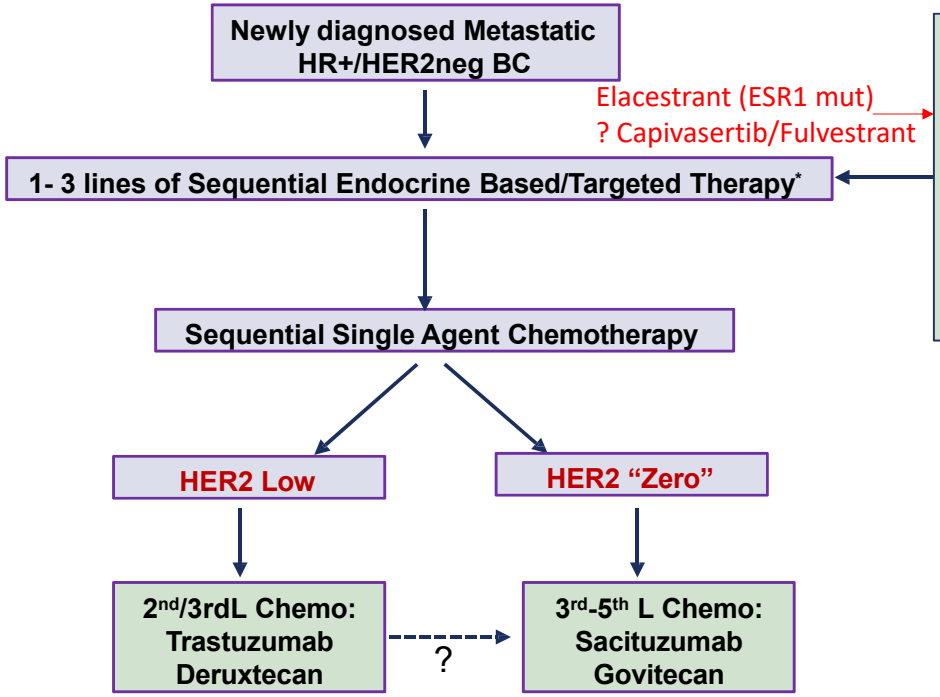
Patient/tumour characteristics	Prior CDK4/6i therapy	Guardant 360 ctDNA
80% postmenopausal	Palbo 90%	54% *ESR1* alteration
60% visceral disease	Prior CDK4/6i for >12m in 75%	35% *PIK3CA* alteration
15% 1 prior chemo for MBC	88% went straight from prior CDK4/6i to PACE	11% *RB1* alteration

	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

Combining palbociclib with fulvestrant beyond progression on prior CDK4/6i did not significantly improve PFS compared with using fulvestrant alone.

Mayer E et al. SABCS 2022, #GS3-06

Treatment Roadmap for HR+/HER2- MBC Today in Clinic



1st L: - AI/SERD + CDK4/6i

2nd or 3rd L: - SERD + PI3Ki (*PIK3CA mutant*)
- ET + mTORi
- SERD + CDK4/6i

1-3rd L: - *gBRCA1/2+: PARPi*

≥2nd L: - *Larotrectinib/Entrectinib (NTRK fusion)*
- *Pembrolizumab (MSI-H/dMMR, High TMB)*

*Chemotherapy for visceral crisis

Courtesy of Dr. Komal Jhaveri, MD FACP

Thank You!

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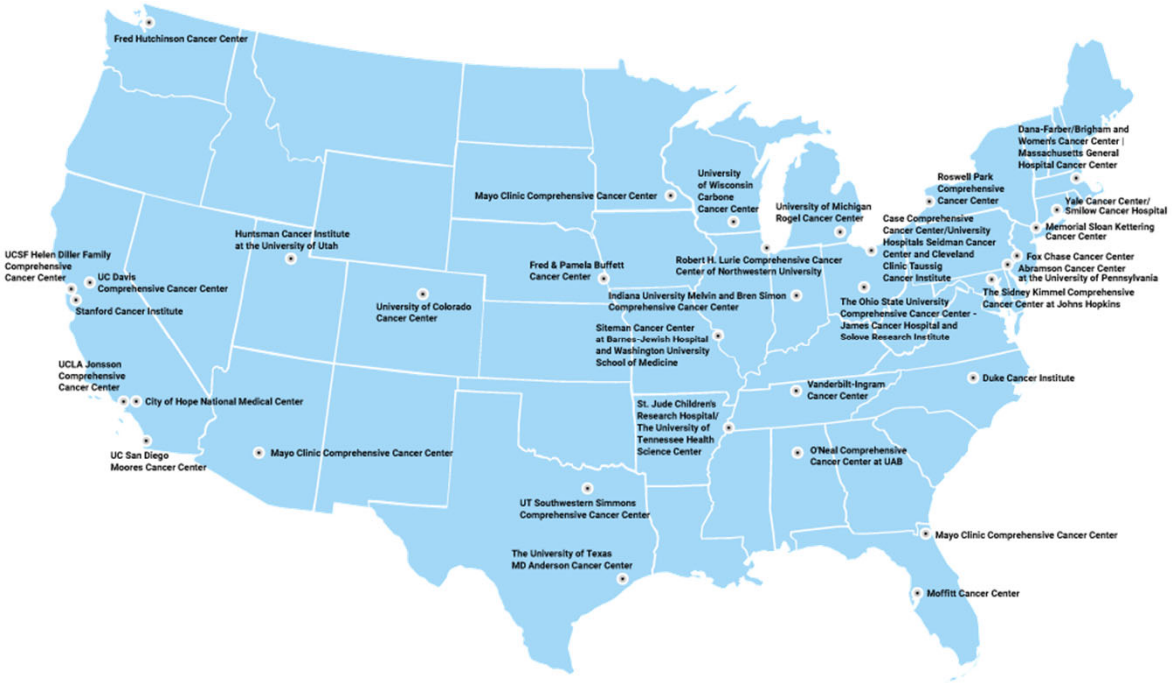
Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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NCCN 2023 BREAST CANCER CONGRESS
with Updates from the 2022 San Antonio Breast Cancer Symposium

Advances in the Management of Metastatic Breast Cancer with SABCS Updates

HR-Negative, HER2-Negative Metastatic Breast Caner

Hatem Soliman, MD

Moffitt Cancer Center

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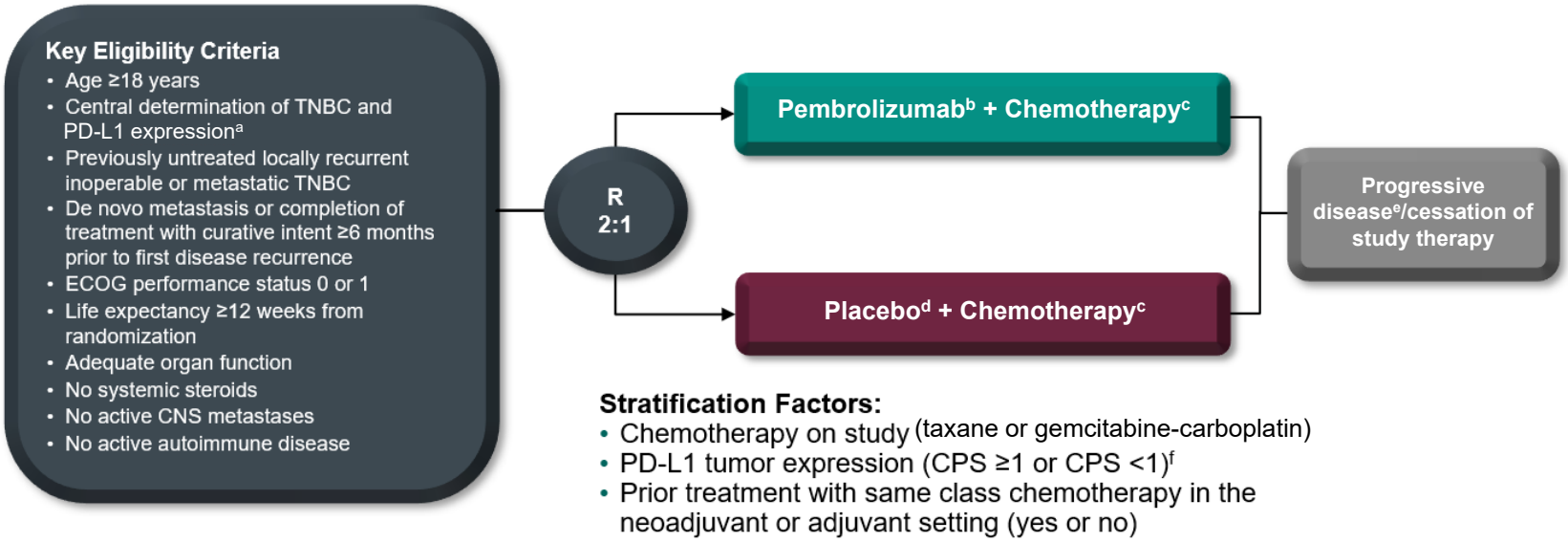
Objectives

- Describe the current therapeutic approaches for first-line management of metastatic HR-negative, HER2-negative metastatic breast cancer.
- Utilize evidence-based approaches to select first- and subsequent-line treatment options for patients with metastatic HR-negative, HER2-negative metastatic breast cancer.
- Outline new and emerging therapeutic options for HR-negative, HER2-negative metastatic breast cancer.

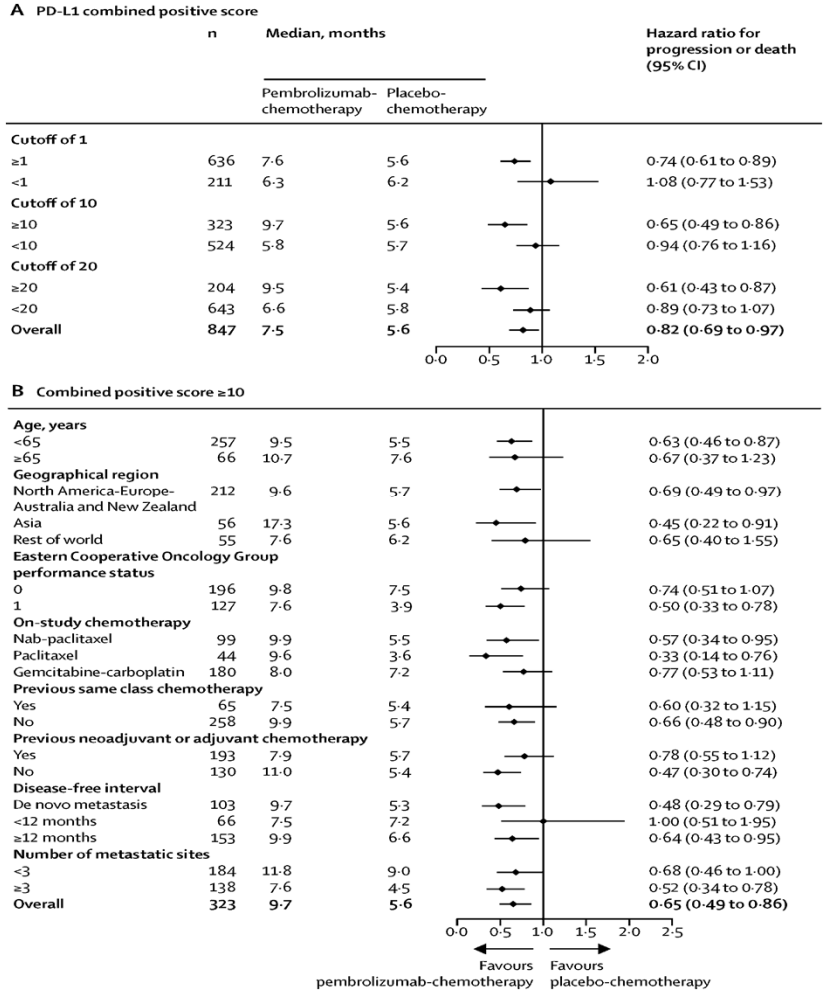
First line metastatic TNBC

- Critical factors to assess include disease burden, organ function, prior treatment history if not de novo particularly DFI from prior treatment
- Clinically actionable testing for 1st line therapy
  - PDL1 CPS score (pembrolizumab)
  - Germline testing for pathogenic BRCA mutations (PARP inhibitors)
- Priority is to utilize pembrolizumab as early as possible based on KEYNOTE-086 data
  - Cohort A pretreated response rate ~5%
  - Cohort B metastatic treatment naïve response rate ~21%

KEYNOTE-355 Study Design (NCT02819518)



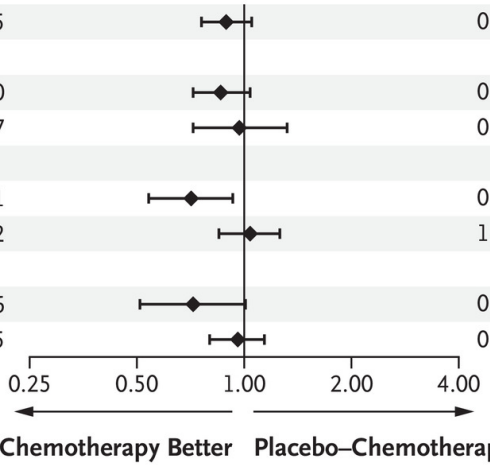
Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)



Cortez et al. *The Lancet* 2020

Pembrolizumab for 1st metastatic TNBC

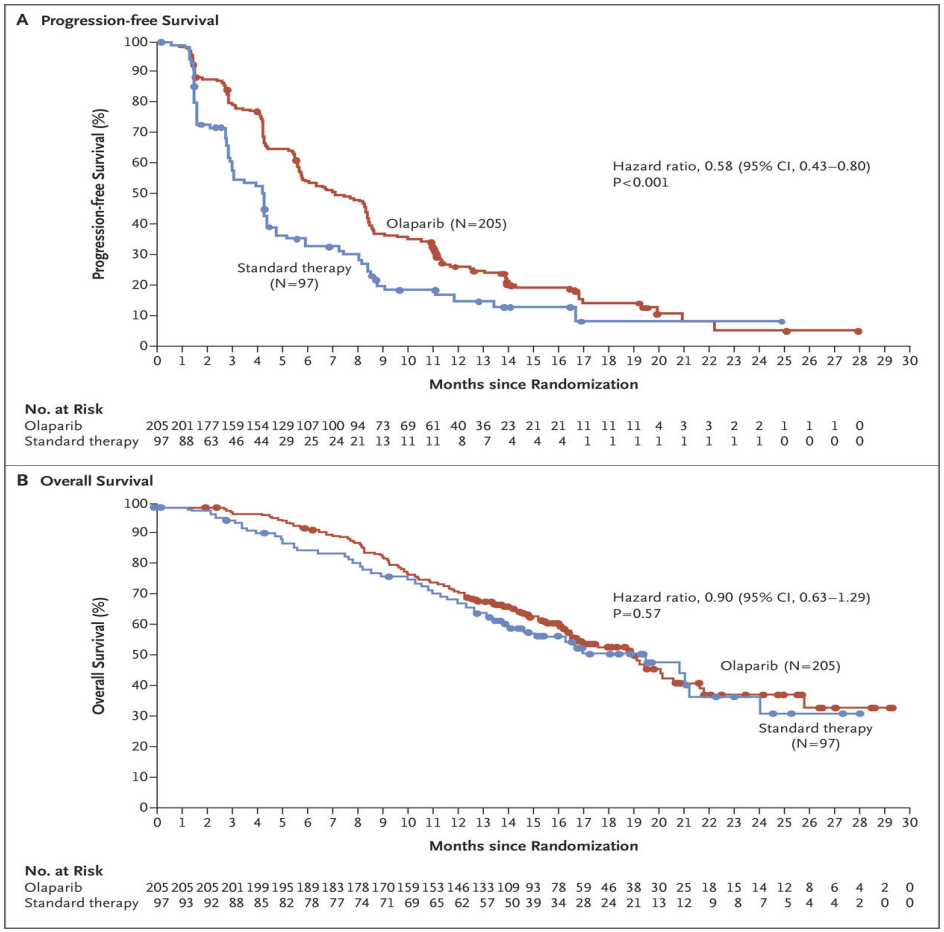
Subgroup	No. of Patients	Median Overall Survival		Hazard Ratio for Death (95% CI)
		Pembrolizumab–chemotherapy	Placebo–chemotherapy	
		mo		
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)



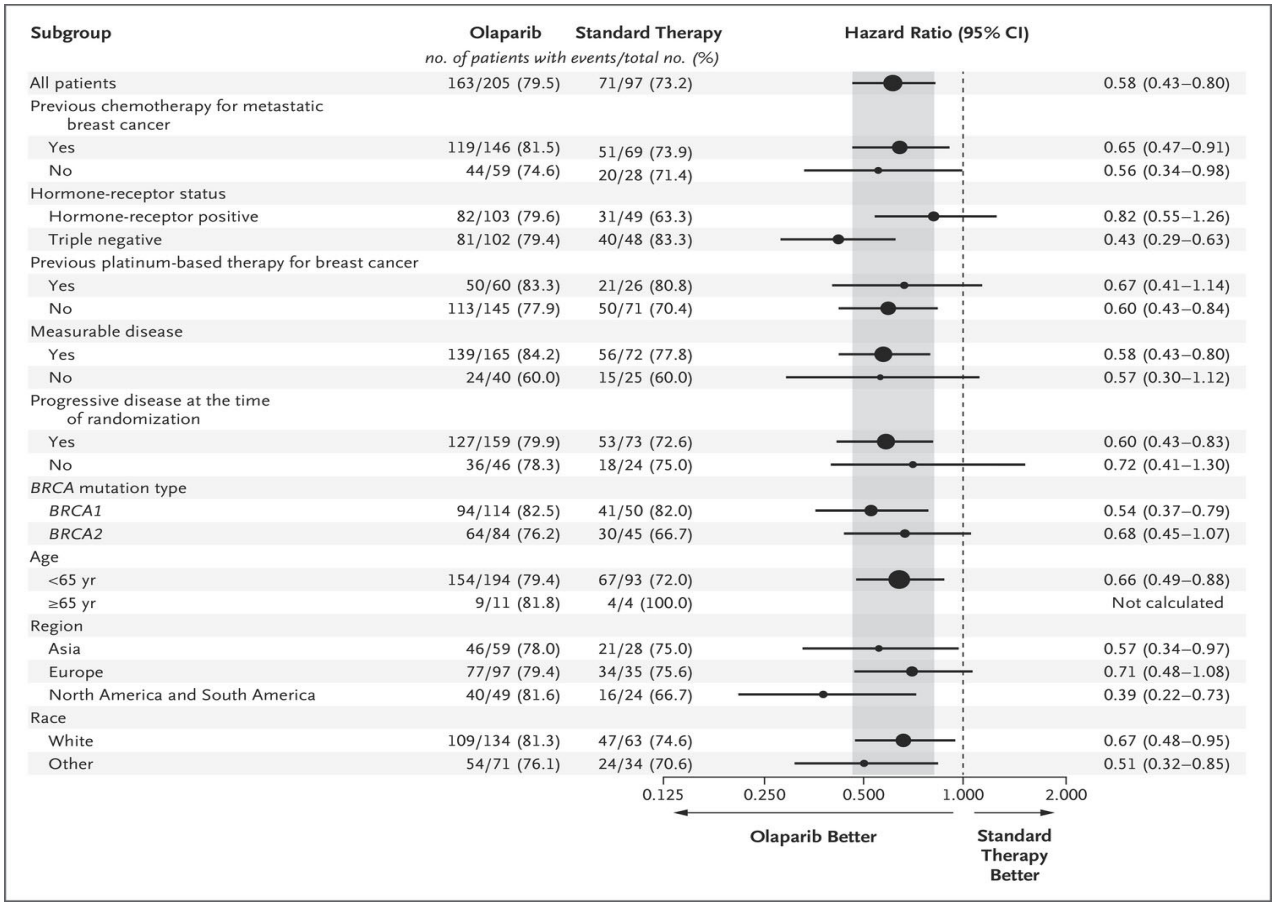
Cortez et al. N Engl J Med 2022; 387:217-226

Olaparib in germline BRCA mutated breast cancer

- OlympiAD trial phase 3 in HER2- BRCA 1/2 germline mutated metastatic breast cancer
- No more than 2 prior lines of chemotherapy
- Randomized 2:1 to olaparib 300mg PO BID or SOC (capecitabine, eribulin, or vinorelbine)
- Powered to show PFS HR .635 with 90% power at 5% significance



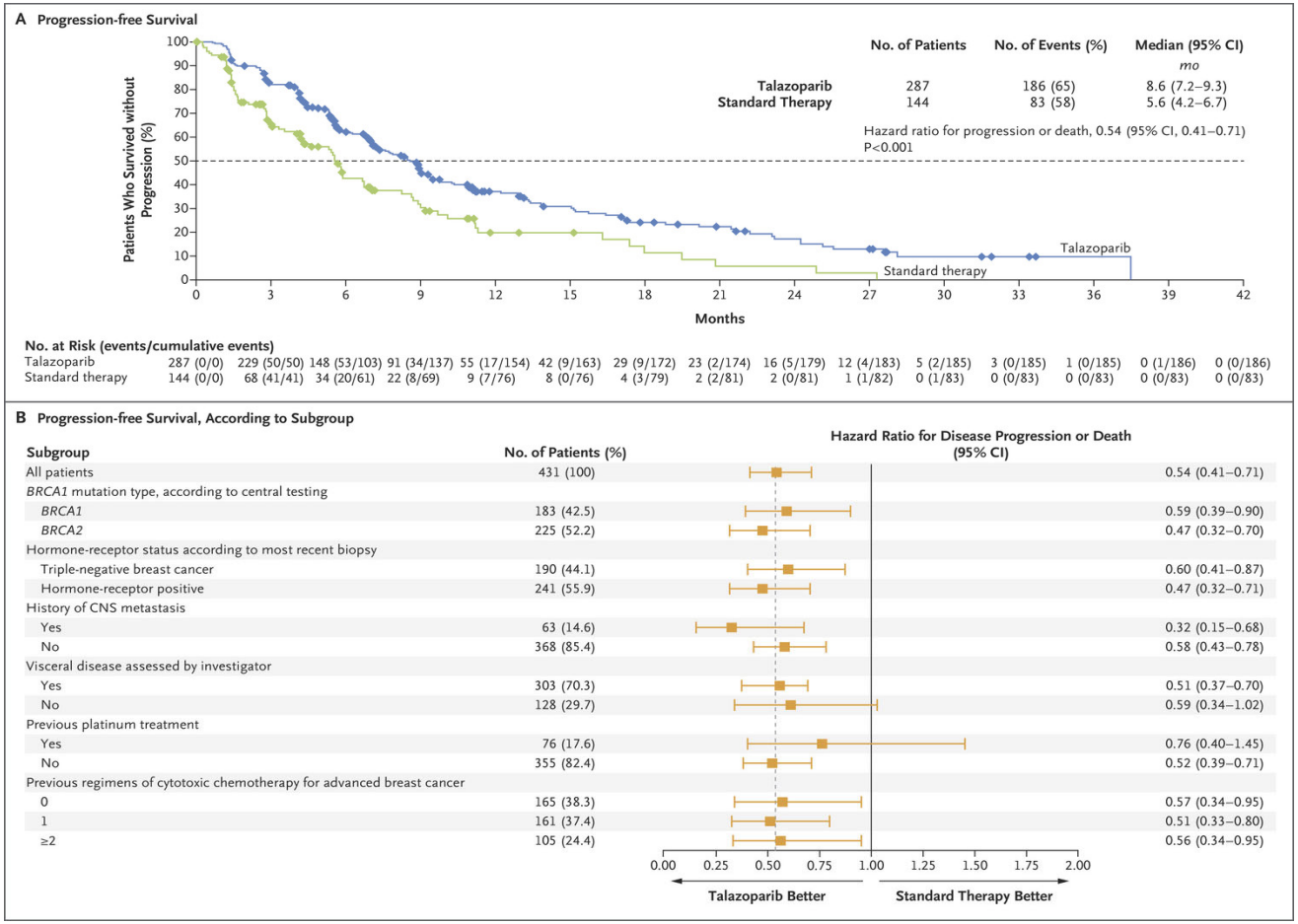
Robson M et al. N Engl J Med 2017;377:523-533.



Robson M et al. N Engl J Med 2017;377:523-533.

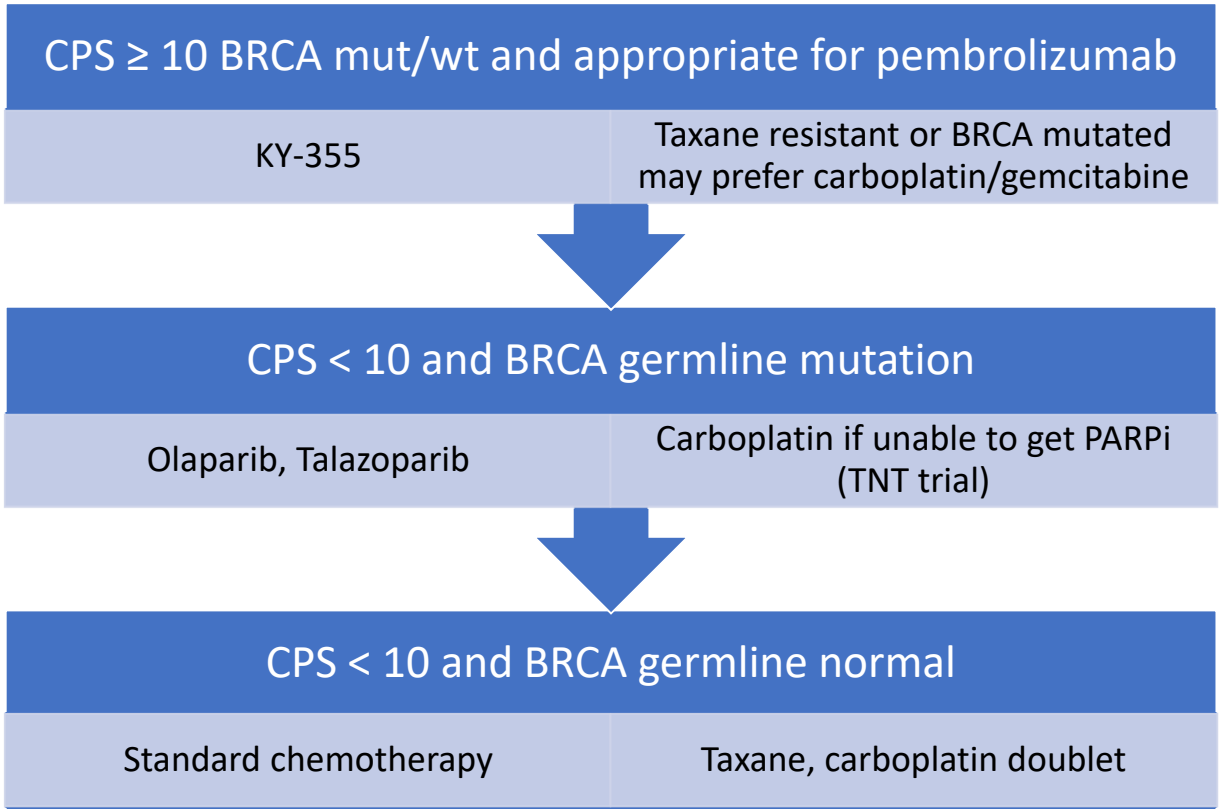
Talazoparib in germline BRCA mutated breast cancer

- EMBRACA trial phase 3 in HER2- BRCA 1/2 germline mutated metastatic breast cancer
- No more than 3 prior lines of chemotherapy, taxane and anthracycline exposed
- Randomized 2:1 to talazoparib 1 mg PO QD or SOC (capecitabine, eribulin, gemcitabine, or vinorelbine)
- Powered to show PFS HR .67 with 90% power at 5% significance



JK Litton et al. N Engl J Med 2018;379:753-763.

Summary of 1st line TNBC Treatment



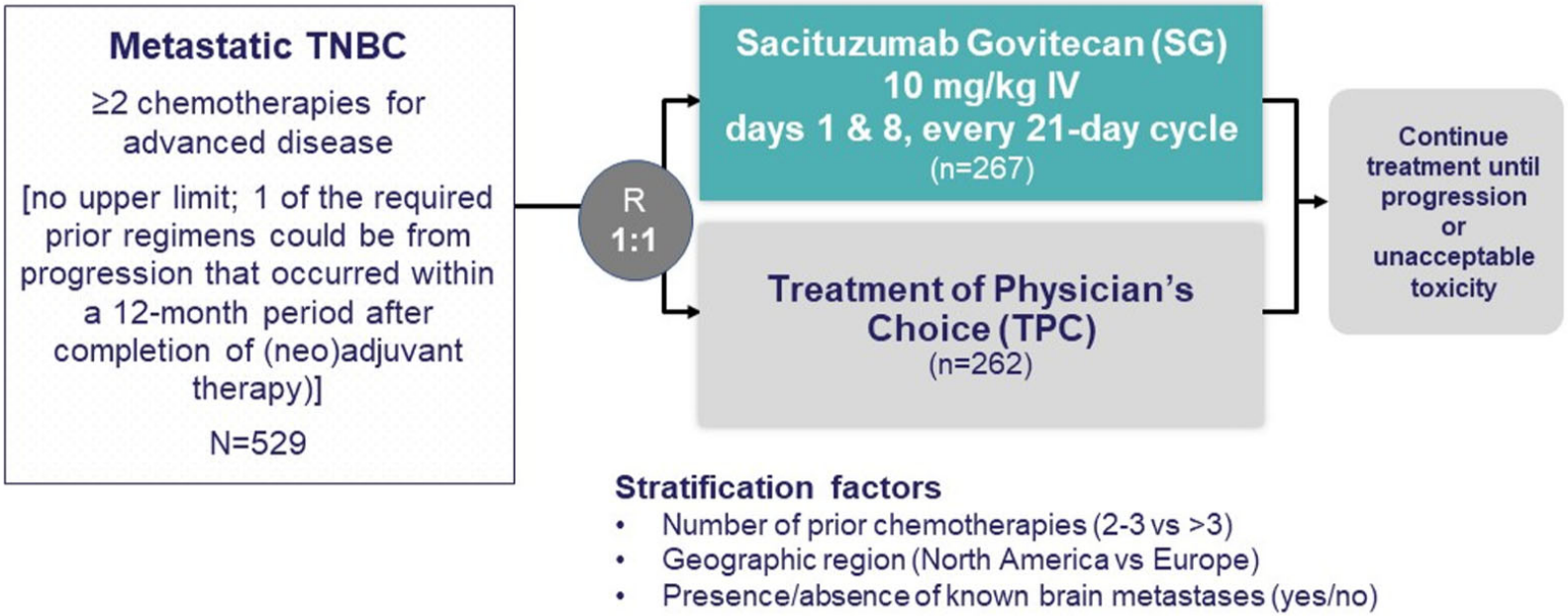
Second line TNBC therapy options and beyond

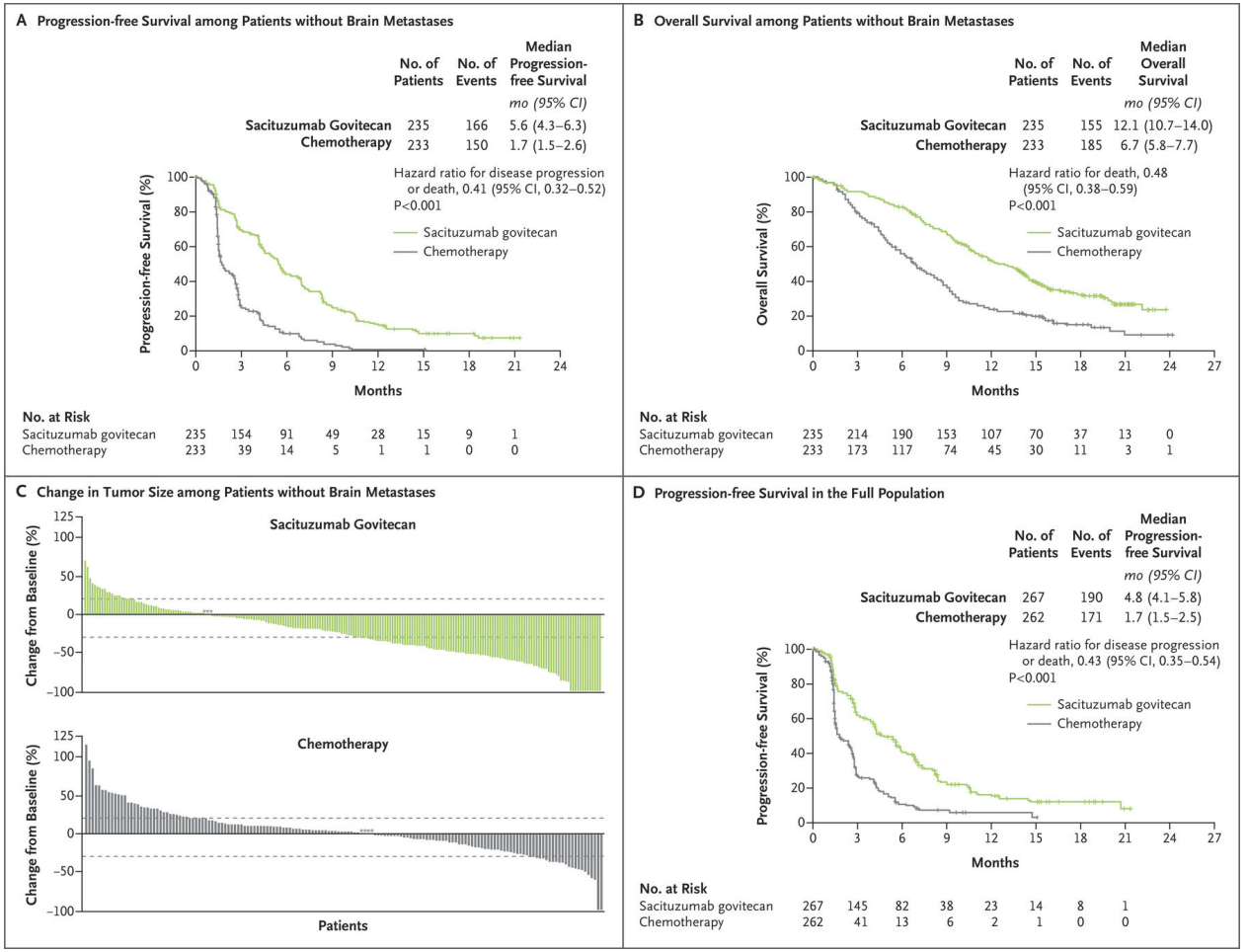
Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative[a,s,t,u]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

- **For specific lines of systemic therapy options for HR-positive and HER2-negative with visceral crisis or endocrine refractory, see BINV-Q (1).**
- **For specific lines of systemic therapy options for HR-negative and HER2-negative (TNBC), see BINV-Q (2).**
- **For specific lines of systemic therapy options for HR-negative or -positive and HER2-positive, see BINV-Q (3).**

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer (Version 4.2022). BINV-Q, 5 of 14.

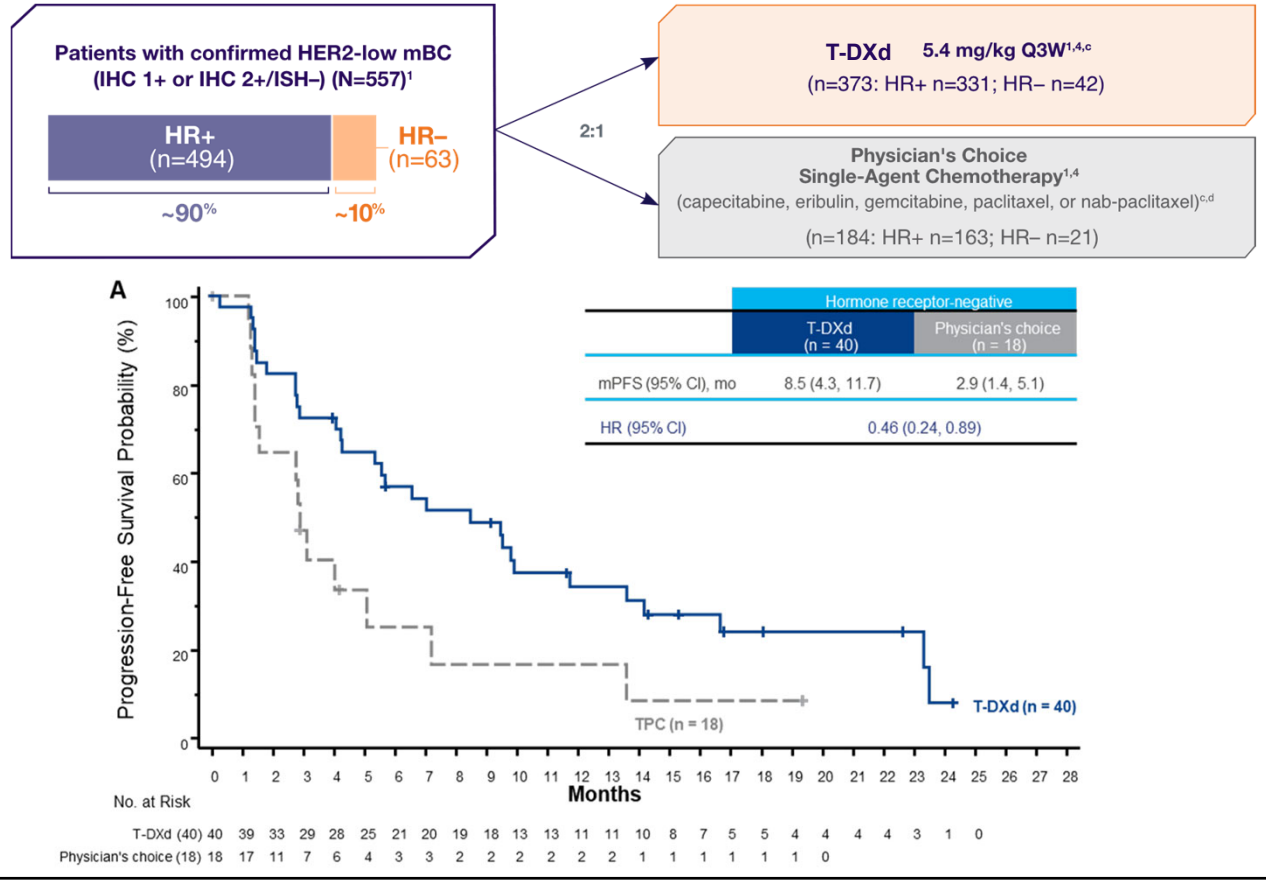
ASCENT TRIAL

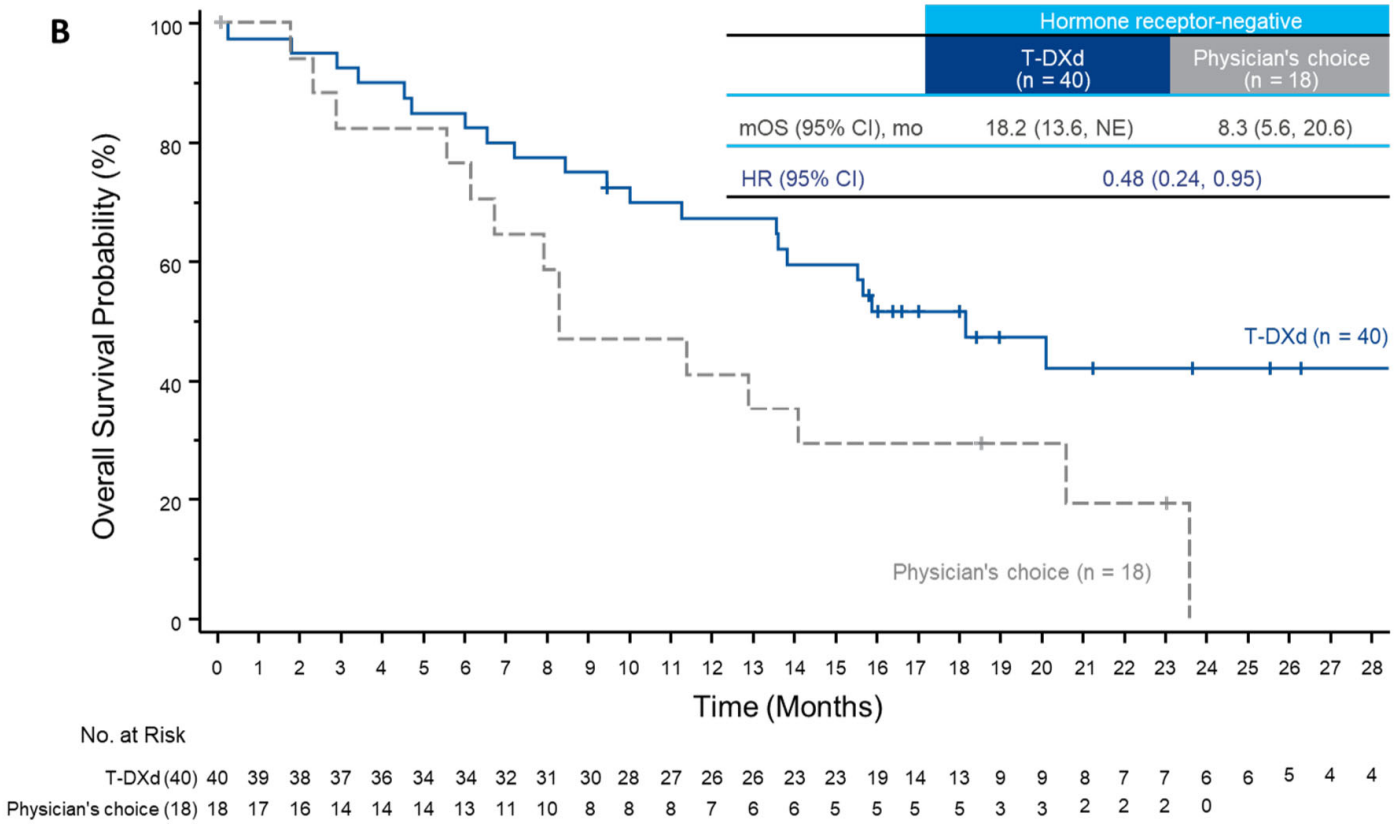


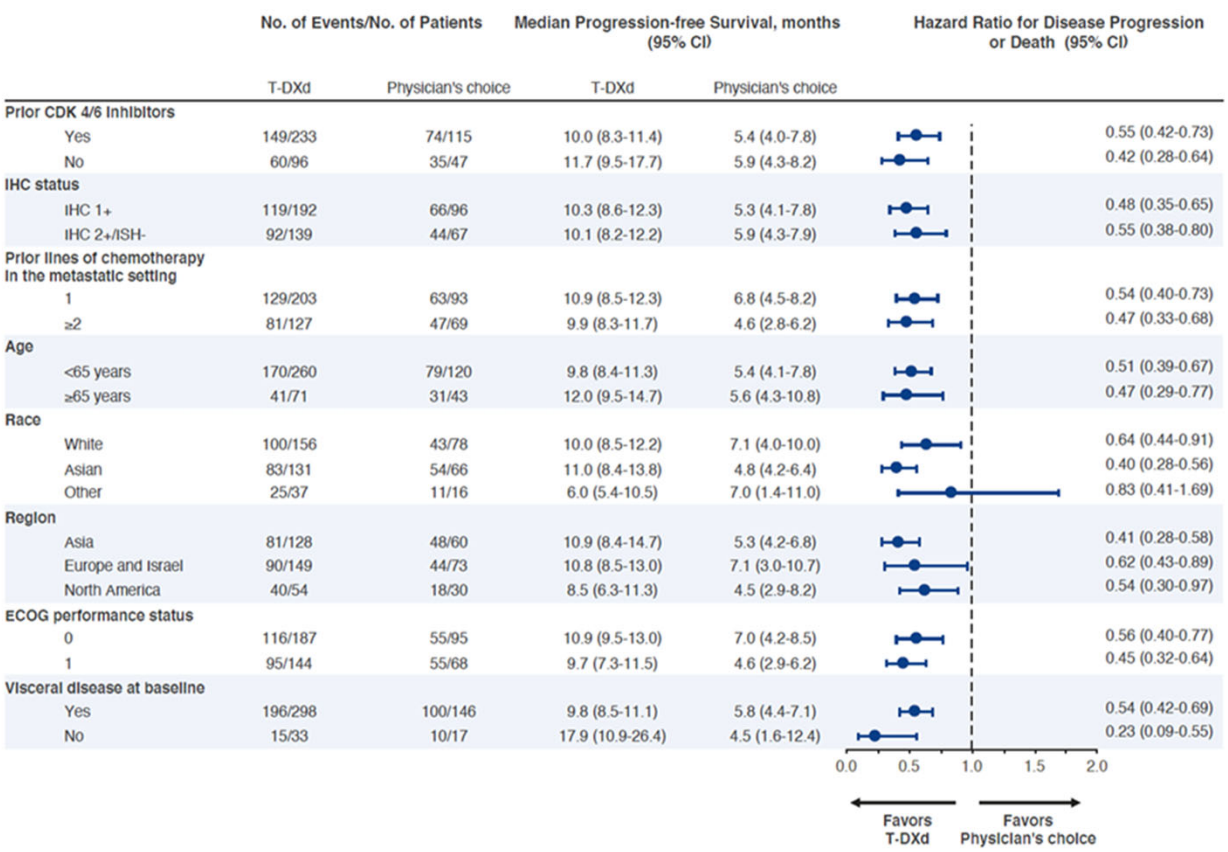


Bardia et al. N Engl J Med 2021; 384:1529-1541

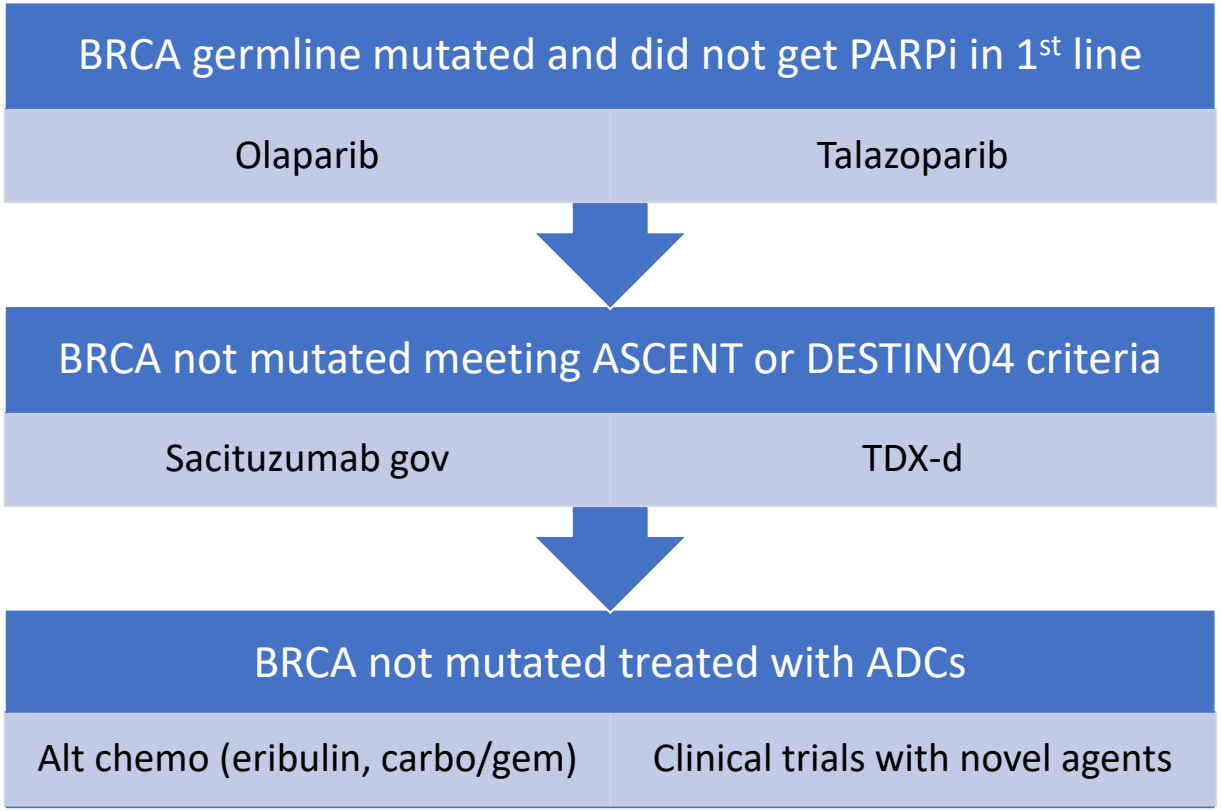
DESTINY-04 TRIAL







Selection of 2nd line and beyond for mTNBC



SABCS 2022 Metastatic TNBC Updates

- BEGONIA phase 1b/2 trial update shows combination of TDX-d plus durvalumab has ORR 56.9% and median PFS of 12.6 months in 1st line TNBC HER 1-2+ patients. No new safety signals. PD11-08 (Schmidt)

- BEGONIA phase 1b/2 trial update shows that combination of datopotamab deruxtecan plus durvalumab is active in 1st line TNBC with ORR of 73.6% and adverse events consistent with each of the agents' safety profiles. Follow up is immature at time of reporting. PD11-09 (Schmidt)

Conclusions

- Prioritization of checkpoint therapy early in CPS 10 or greater patients
- Identification of patients with particularly gBRCA mutations important for PARPi selection. Somatic mutations or alternative DDR mutations such as PALB2 may be considered
- ADCs will likely be important agents and may move up the therapeutic sequence as activity is high. TBD how efficacy will be impacted if multiple ADCs with similar payloads/targets are used sequentially.
- Must continue to prioritize novel agents for TNBC aggressively!

National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

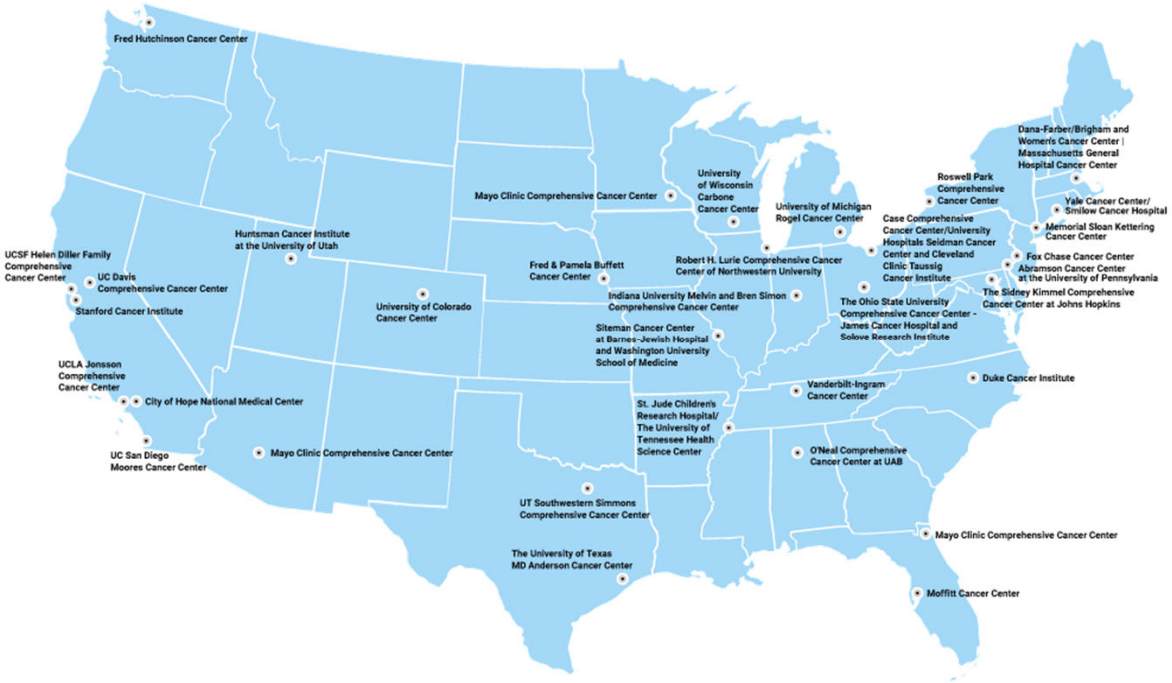
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal

NCCN 2023 BREAST CANCER CONGRESS
with Updates from the 2022 San Antonio Breast Cancer Symposium

Advances in the Management of Metastatic Breast Cancer with SABCS Updates

HER2-Positive Metastatic Breast Caner

William J. Gradishar, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

National Comprehensive Cancer Network®

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[j]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[k]	Pertuzumab + trastuzumab + docetaxel[l,m]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[m]	Preferred Regimen	2A
Second line[l]	Fam-trastuzumab deruxtecan-nxki[i,n,o]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[l]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[m,p]	Other Recommended Regimen[p]	1
	Trastuzumab + docetaxel or vinorelbine[m,q]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[m,q]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[m,q]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[m,q] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[m,q,r,s]	Other Recommended Regimen	2A
	Neratinib + capecitabine[q]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[q] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	**Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)**
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	**Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)**
Third Line	**Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)**
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	**Trastuzumab + docetaxel or vinorelbine**
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

[j] See additional considerations for those receiving systemic HER2-targeted therapy (BINV-Q 4).

[k] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.

[l] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).

[m] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.

[o] May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.

[p] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.

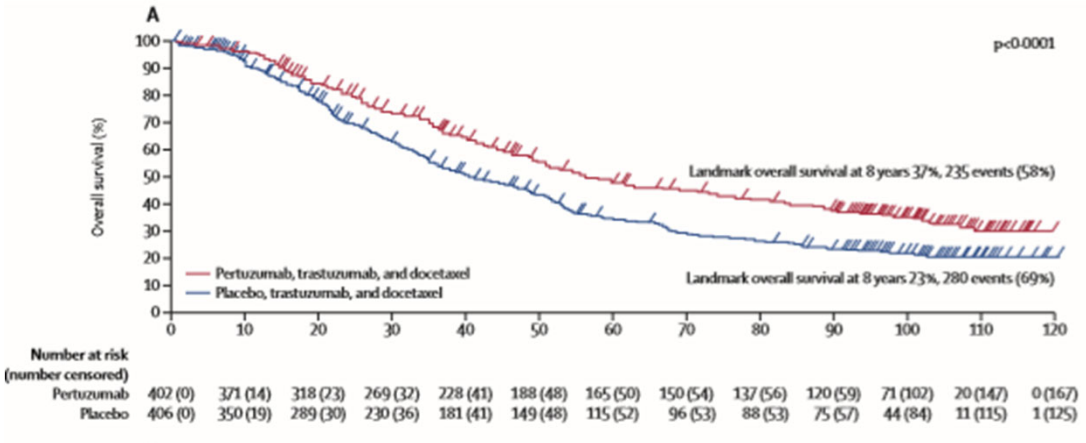
[q] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[r] Trastuzumab may be safely combined with all non-anthracycline–containing preferred and other single agents listed on (BINV-Q 5) for recurrent or metastatic breast cancer.

CLEOPATRA: End-of Study Results

Median follow-up was 99·9 months in the pertuzumab group (IQR 92·9–106·4) and 98·7 months (90·9–105·7) in the placebo group

End-of-Study OS in ITT Population*



*Crossover patients were analyzed in the placebo arm.

	Median OS, Mos (95% CI)
Pertuzumab + Trastuzumab/Doc	**57.1**
Placebo + Trastuzumab/Doc	**40.8**

Swain SM et al. *Lancet Oncol* 2020; 21: 519–30.

T-DM1: Standard Second-Line Therapy

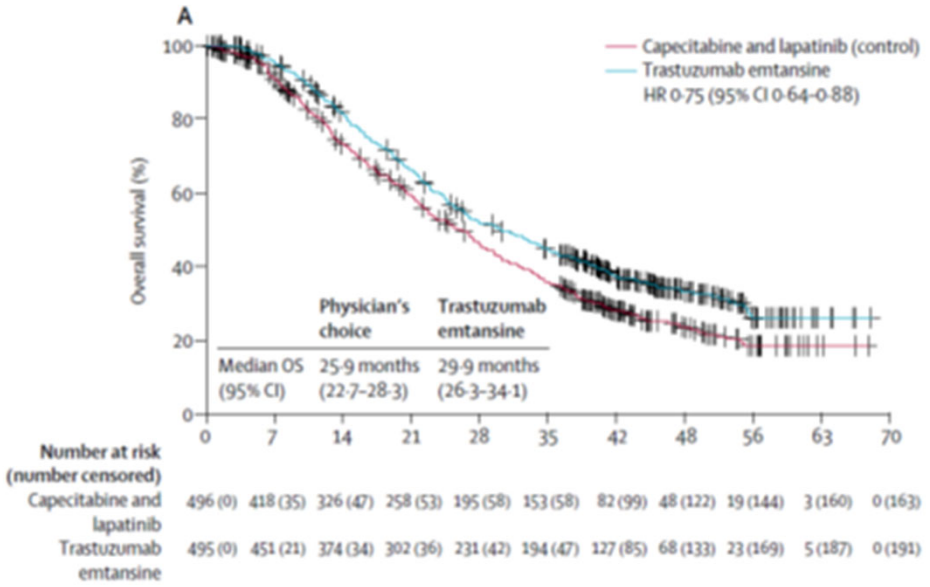
HER2+ (central) LABC or MBC (N = 980)

- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mo of adjuvant tx

1:1

- **T-DM1**
- **Capecitabine + Lapatinib**

EMILIA

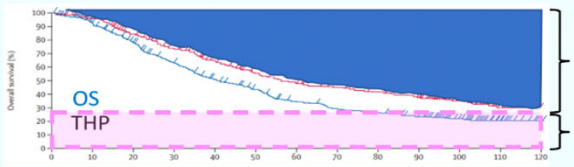


Overall Survival

Dieras V, et al. *Lancet Oncol*. 2017;18:732-742.

Why do we need more anti-HER2 treatment options?

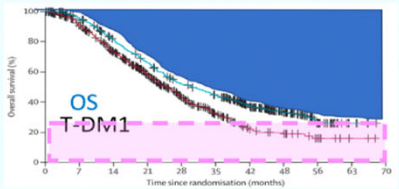
CLEOPATRA [1,2]



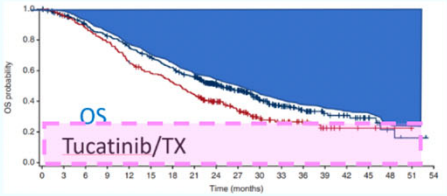
The losses we want to prevent

The plateau we want to expand and consolidate

EMILIA [3,4]



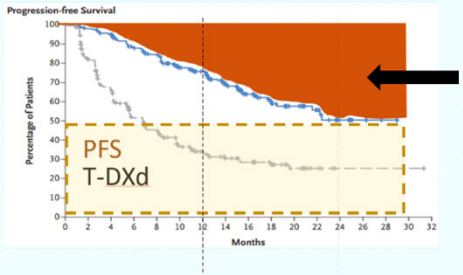
HER2Climb [5,6]



Adapted from: 1. Swain SM, et al. Lancet Oncol 2020; 2. Swain SM, et al. N Engl J Med 2015; 3. Dieras V, et al. Lancet Oncol 2017; 4. Verma S, et al. N Engl J Med 2012; 5. Murthy R, et al. N Engl J Med 2020; 6. Curigliano G, et al. Ann Oncol 2022

Why do we need more anti-HER2 treatment options?

DestinyBREAST-03 [1]



Estimate post-T-DXd treatment will be needed when T-DXd is used in second line:
- In 25% of patients after 1yr
- In 50% of patients after 2yr

1. Adapted from Cortes J, et al N Engl J Med 2022

Clinical Trial Design (Phase III- Destiny-Breast03)

Destiny-Breast 03 Study

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

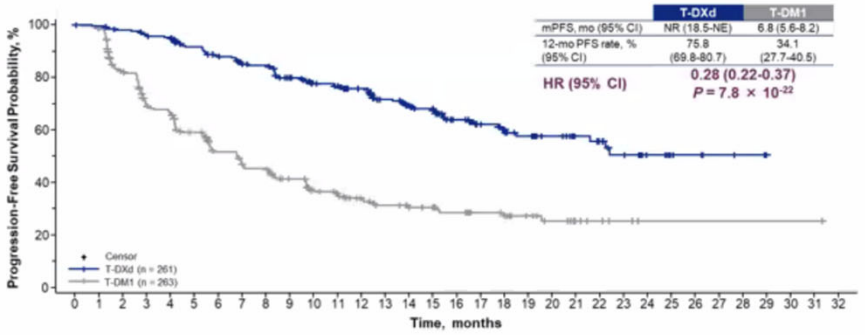
Stratification factors

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

R 1:1

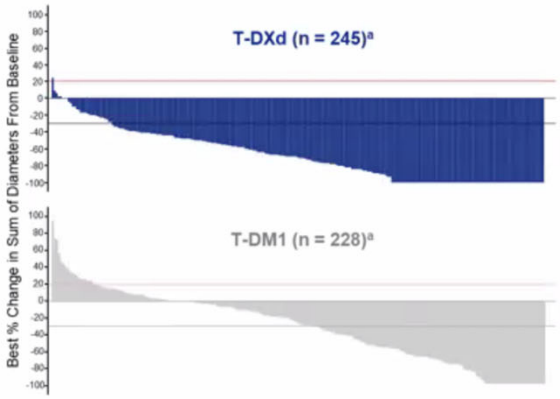
- T-DXd 5.4 mg/kg Q3W (n = 261)
- T-DM1 3.6 mg/kg Q3W (n = 263)

PFS



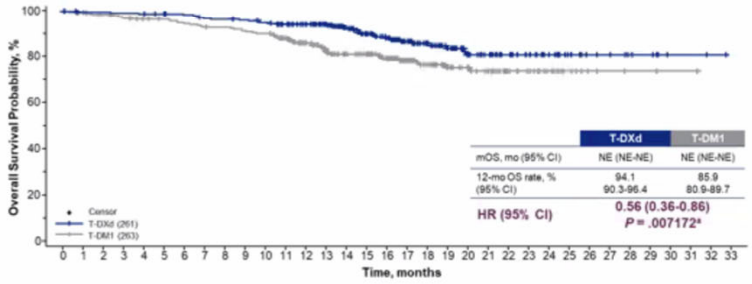
	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

ORR



	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)

OS

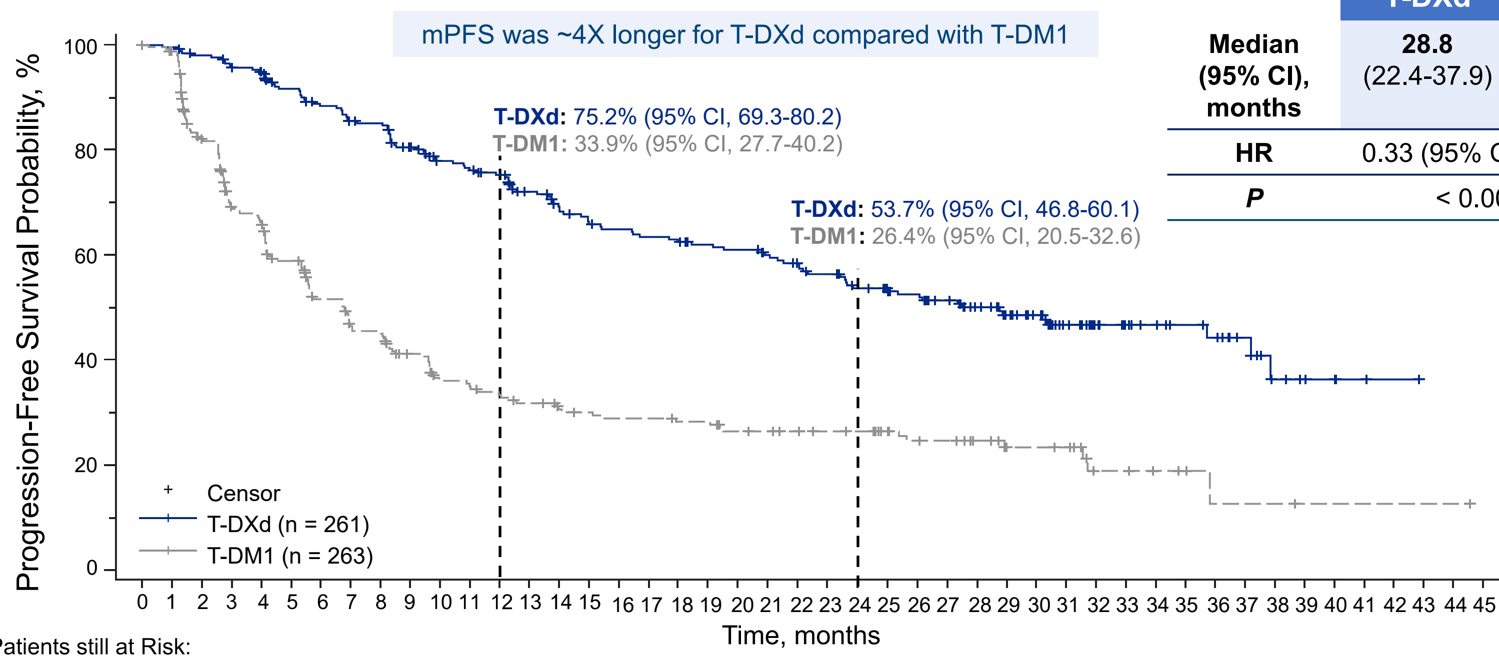


	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 (90.3-96.4	85.9 (80.9-89.7
HR (95% CI)	0.56 (0.36-0.86)	
	$P = .007172$[a]	

Cortes J, et al. ESMO 2021

DESTINY-Breast03

Updated Primary Endpoint: PFS by BICR



	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:

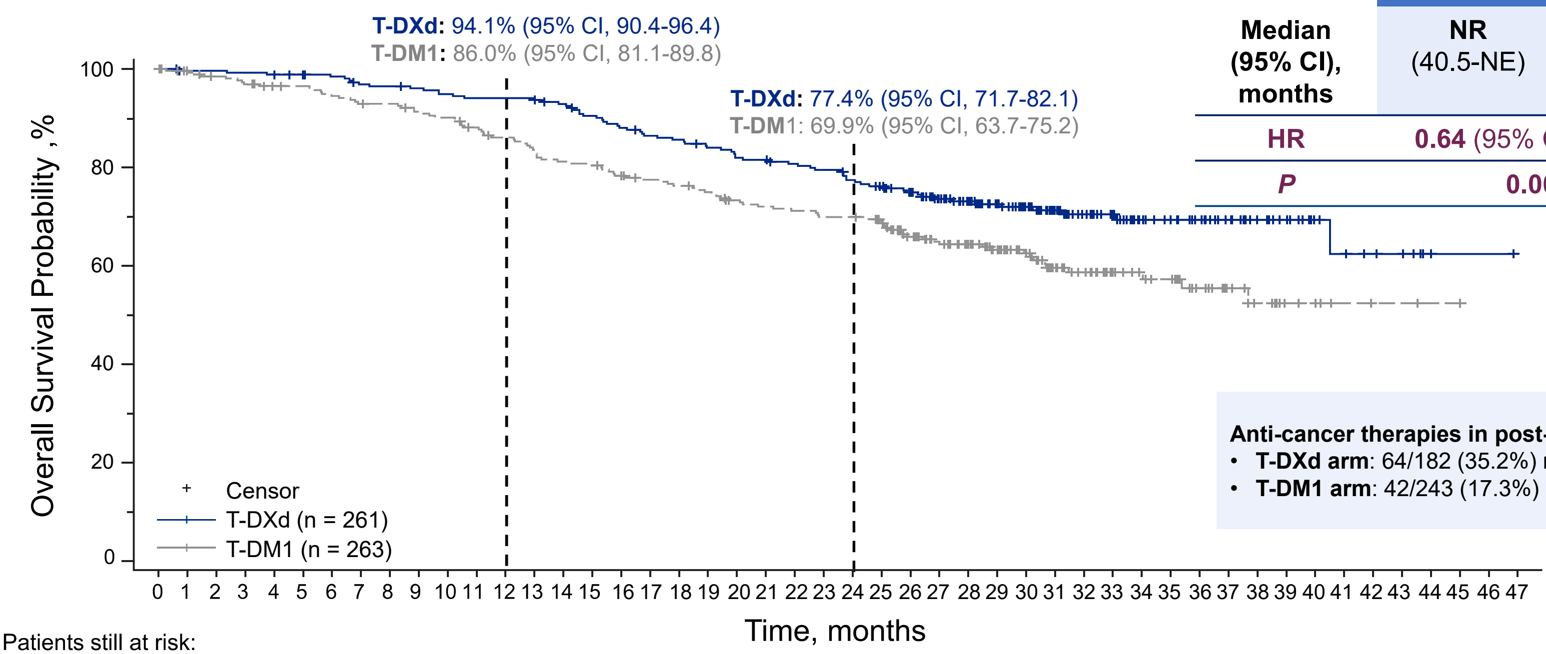
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39

	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
T-DXd	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

Hurvitz S, GS2-02, SABCS 2022

DESTINY-Breast03

Key Secondary Endpoint: Overall Survival



	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Anti-cancer therapies in post-trial setting:

- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Patients still at risk:

Time, months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164

Time, months	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

Hurvitz S, GS2-02, SABCS 2022

DESTINY-Breast03

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

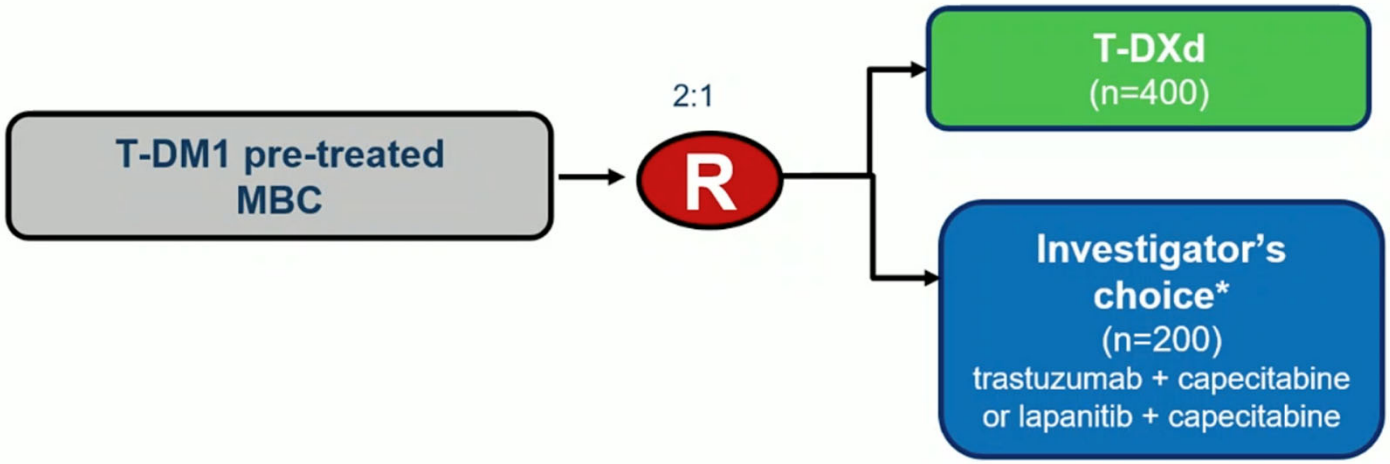
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

Hurvitz S, GS2-02, SABCS 2022

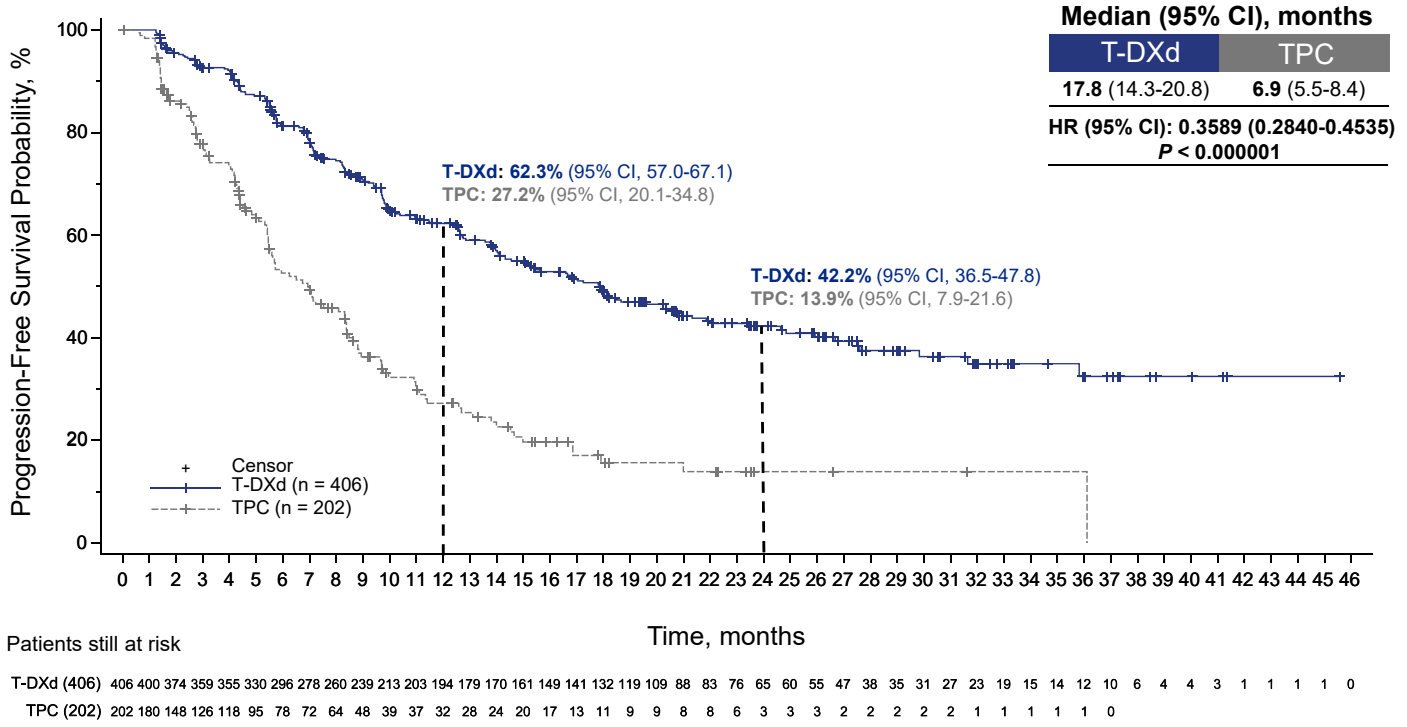
1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

DESTINY-Breast02 Trial for HER2+ MBC



Positive Trial for Dual Primary Endpoints of PFS and OS!

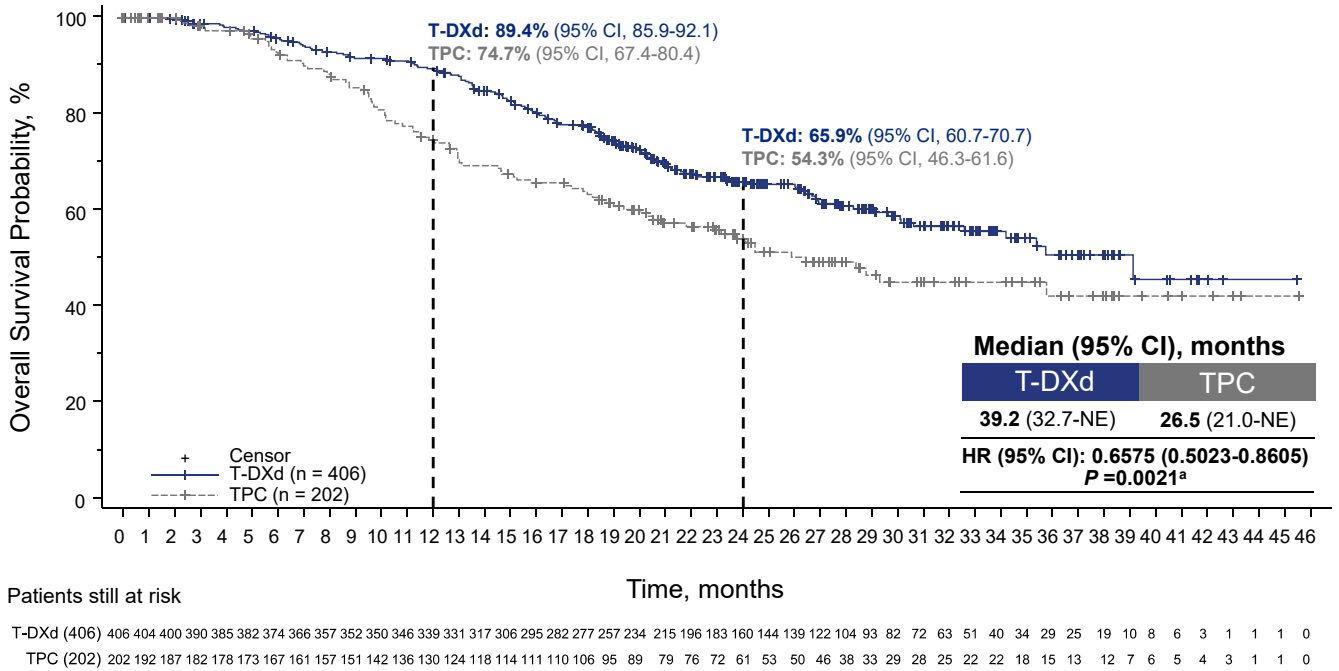
Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Krop I, SABCS 2022. GS2-01

Key Secondary Endpoint: OS



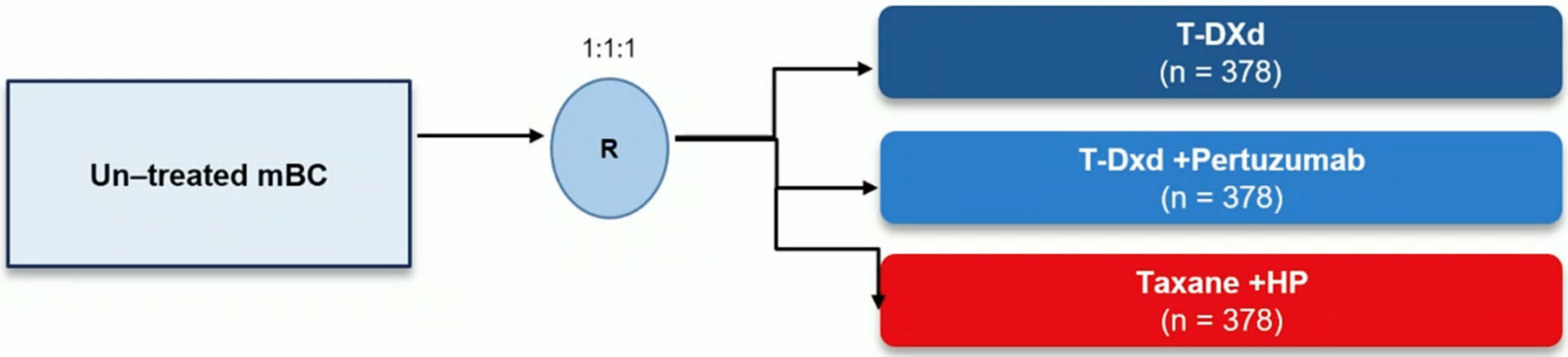
In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Krop I, SABCS 2022. GS2-01

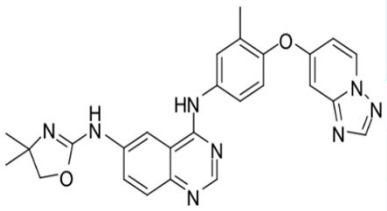
DESTINY Breast-09 Trial : 1st Line HER2+ MBC



Primary endpoint: PFS

HER2CLIMB Pivotal Trial Design: Capecitabine/Trastuzumab +/- Tucatinib

Tucatinib



Compound	Cellular Selectivity Data	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
tucatinib	8	>10,000
neratinib	7	8
lapatinib	49	31

Patient Population
- Metastatic HER2+ breast cancer with progression after pertuzumab, trastuzumab, and T-DM1
- Patients with and without brain metastases

2:1
n=480

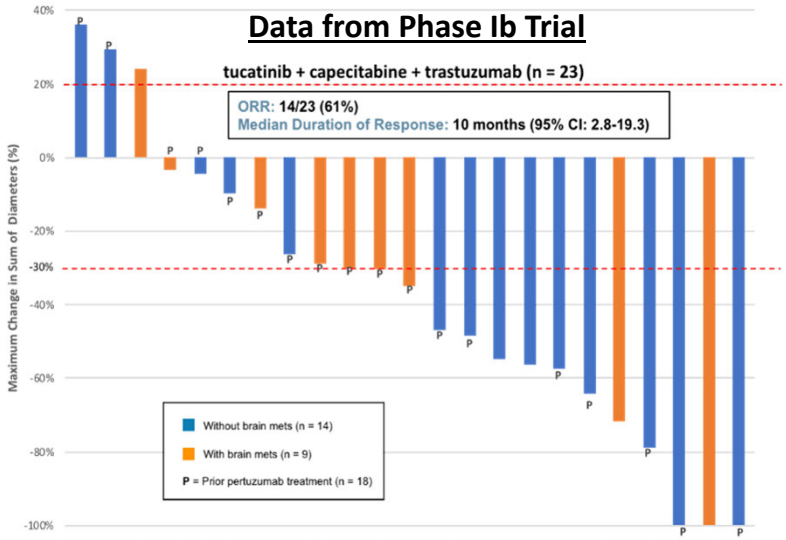
- capecitabine + trastuzumab + tucatinib
- capecitabine + trastuzumab + placebo

Primary endpoint:
- PFS in all pts

Secondary endpoints:
- PFS in pts w/ brain metastases
- OS in all pts

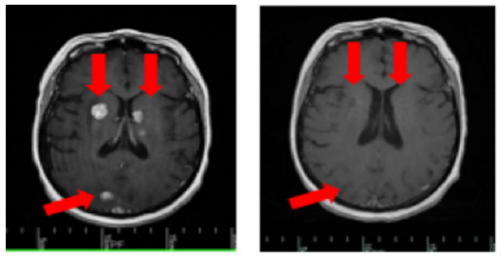
Sample size ↑'ed to N = 612 [NCT02614794]

Data from Phase Ib Trial



Note: Bars represent change in measurable lesions but some patients also have nonmeasurable lesions. In addition, 4 patients in the Triplet cohort had nonmeasurable lesions only and are therefore not able to be represented on the waterfall.

*CNS metastases = 48%
Untreated 22% and
Treated, progressing 18%

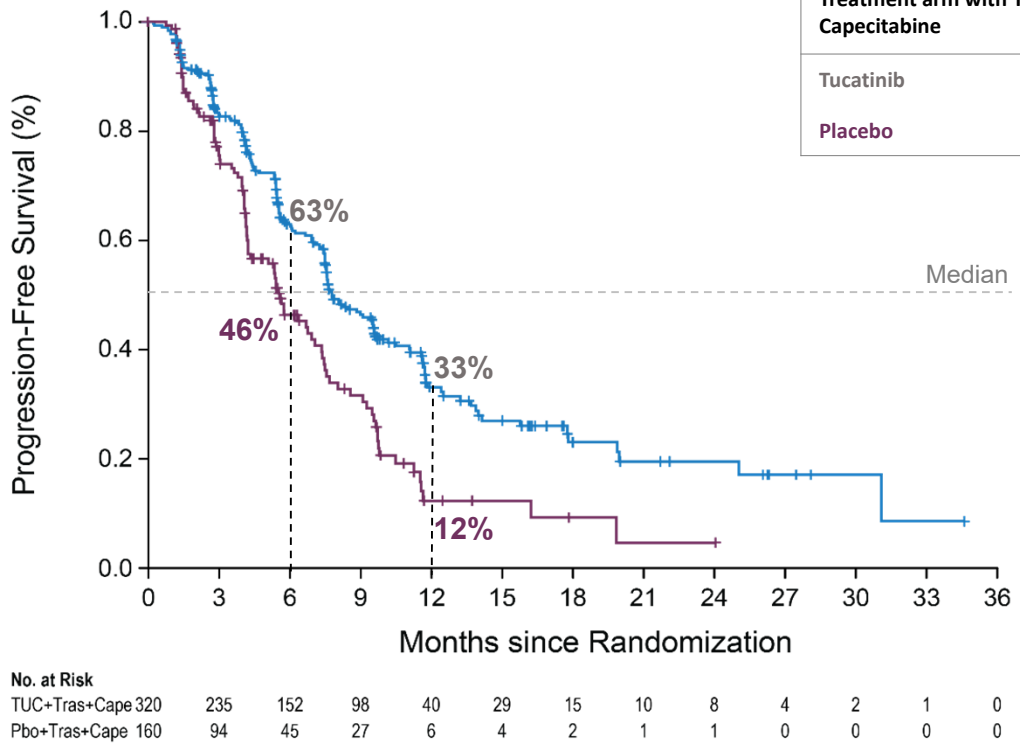


Screening | Post-cycle 6

(Images selected to demonstrate longest axis of lesions)

Murthy R, et al. Lancet Oncology 2018

Progression-Free Survival with Tucatinib Added to Capecitabine and Trastuzumab in HER2+ MBC (Including with Brain Metastases): HER2CLIMB Study Results



Treatment arm with Trastuzumab + Capecitabine	Events, N=480	HR (95% CI)	P Value
Tucatinib	178/320	0.54 (0.42, 0.71)	<0.00001
Placebo	97/160		

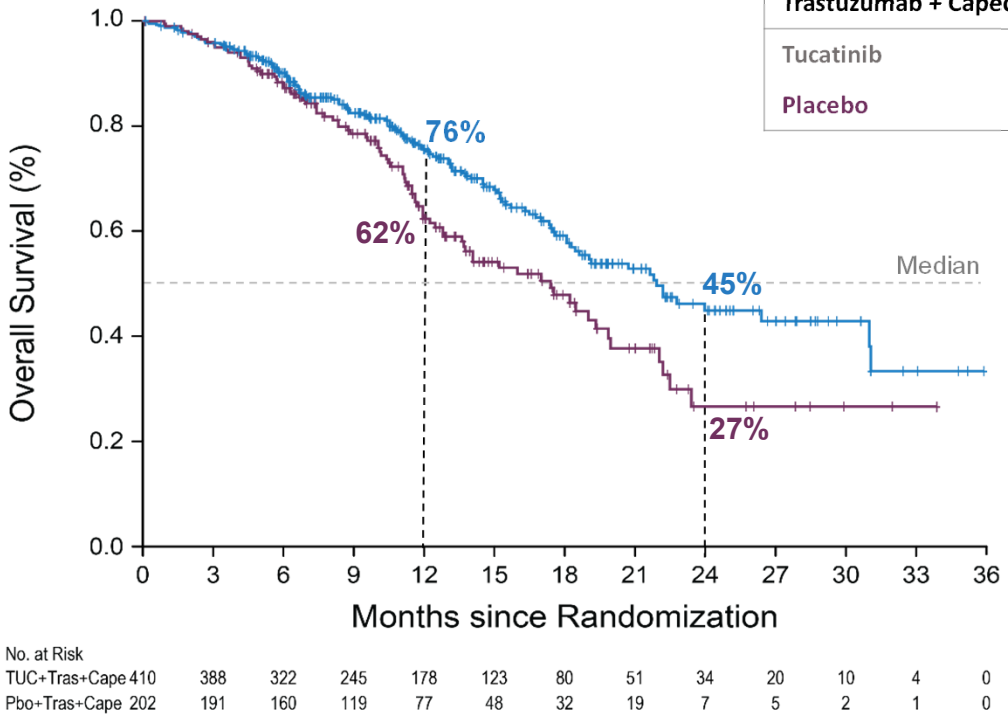
Risk of progression or death was reduced by 46% in the primary endpoint population

One-year PFS (95% CI):	
Tucatinib 33% (27, 40)	**Placebo** 12% (6, 21)
Median PFS (95% CI):	
7.8 months (7.5, 9.6)	**5.6 months** (4.2, 7.1)

Prespecified efficacy boundary for PFS: P=0.05
Data cut off: Sep 4, 2019

Murthy R, et al. NEJM 2019

Overall Survival with Tucatinib Added to Capecitabine and Trastuzumab in HER2+ MBC (Including with Brain Metastases): HER2CLIMB Study Results



Treatment arm with Trastuzumab + Capecitabine	Events N=612	HR (95% CI)	P Value
Tucatinib	130/410	0.66 (0.50, 0.88)	0.00480
Placebo	85/202		

Risk of death was reduced by 34% in the total population

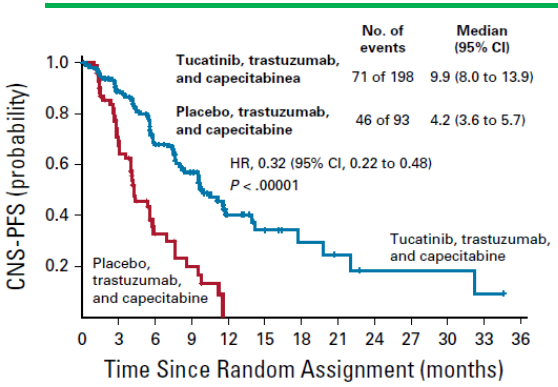
Two-year OS (95% CI):	
Capecitabine 45% (37, 53)	Placebo 27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

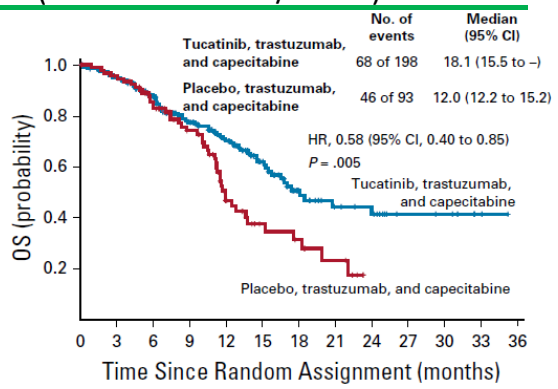
Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

Murthy R, et al. NEJM 2019

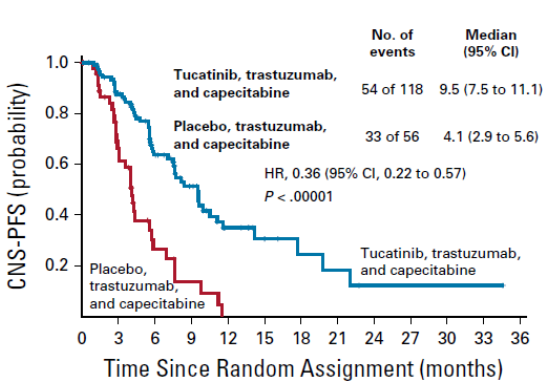
Intracranial CNS-Specific Outcomes: HER2CLIMB Study Results

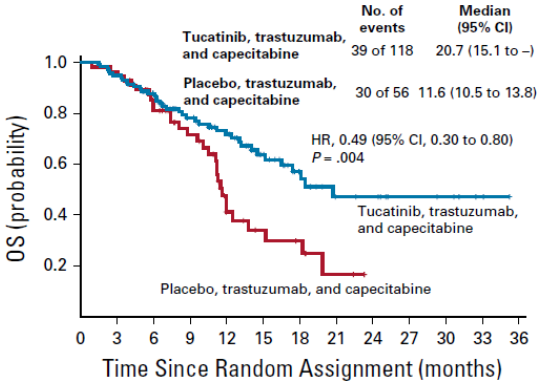
Patient with Brain Metastases (active or treated/stable)





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. JCO 2020

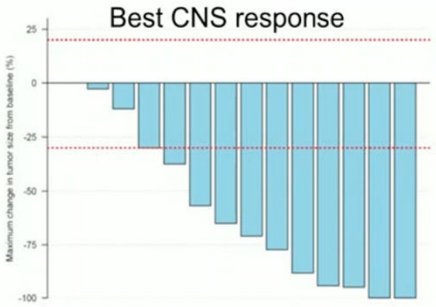
T-DXd in Breast cancer brain metastases

Table 1. Studies on T-DXd in brain metastases from advanced HER2-positive breast cancer.

Study	Type of study	Number of patients with BM	Intracranial response	Intracranial PFS
DESTINY-Breast 01 NCT03248492 (10)	Single-arm phase II	24 with asymptomatic BM	ORR: 58.3% CR: 4.2% PR: 54.2% SD: 33.3%	Median: 18.1 months
DESTINY-Breast 03 NCT03529110 (11)	Phase III randomized (T-DXd vs. T-DM1)	62 (T-DXd arm) and 52 (T-DM1) stable BM	T-DXd arm: • ORR: 63.9% • CR: 27.8% • PR: 36.1% T-DM1 arm: • ORR: 33.4% • CR: 2.8% • PR: 30.6%	T-DXd arm: median: 15.0 months T-DM1 arm: median: 5.7 months
TUXEDO-1 NCT04752059 (12)	Single-arm phase II	15: • 6 stable/untreated BM • 9 active/progressing BM after local therapy	ORR: 73.3% CR: 13.3% PR: 60.0% SD: 33.3% Per protocol population: ORR 78.6%	Median: 14.0 months
DEBBRAH NCT04420598 (13)	Single-arm phase II	21: • Cohort 1: 8 HER2 stable BM after surgery and/or RT • Cohort 2: 4 HER2^{+} asymptomatic untreated BM • Cohort 3: 9 HER2^{+} progressing BM after surgery and/or RT	Cohort 2: • ORR: 50.0% Cohort 3: • ORR: 44%	At 6 months: 78.7%
Kabraji et al. (1)	Retrospective	15 asymptomatic or active/progressing BM	ORR: 73.0% PR: 73.3% SD: 13.3%	Median: 7.0 to not reached 12 months: 74.7%

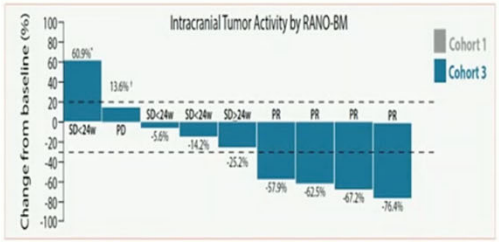
Modi S NEJM 2022; Cortes J NEJM 2022; Bartsch R Nature Med 2022; Perez-Garcia JM Neuro Oncol 2022; Kabraji S Clin Cancer Res 1;2023;

CNS Activity of TDXd in Pts with HER2+ Breast Cancer Brain Metastases



TUXEDO-1 trial
Bartsch et al, ESMO Breast 2022

ORR-IC = **73%** in pts with active BM



DEBBRAH trial
Vaz Batista et al, SABCS 2021

ORR-IC =**44%** in pts with Active BM

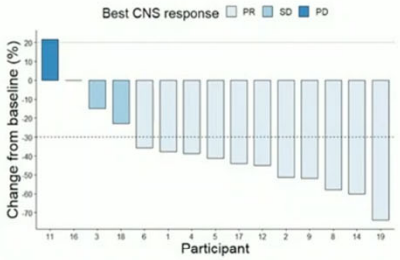


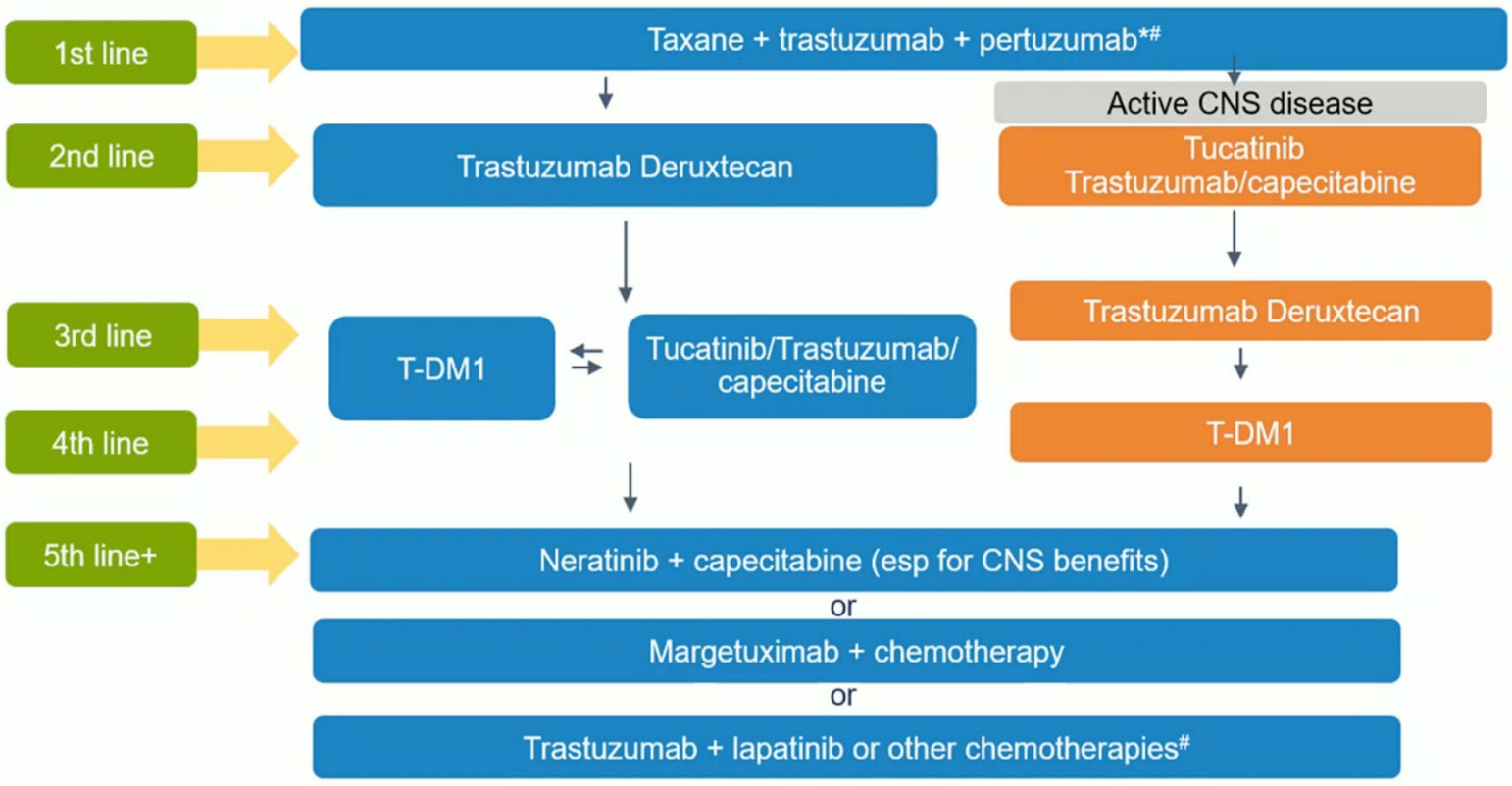
Figure 5 : Best CNS response to T-DXd. Waterfall plot of best CNS response in participants with measurable disease (n = 15). PR = partial response

DFCI/Duke/MDACCC series
Kabraji et al, SABCS 2021

ORR-IC =**73%**
(70% in pts with active BM)

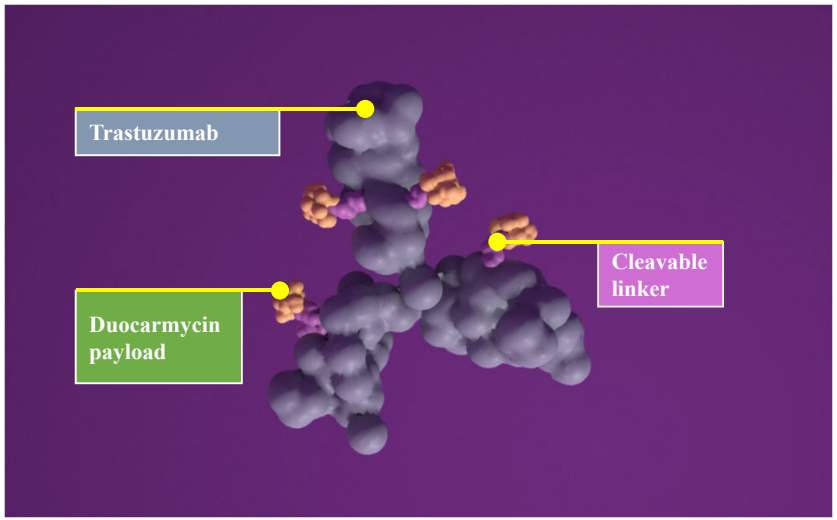
Lin N , ASCO 2022

2023 Approach to Therapy for Metastatic HER2+ BC:



*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Trastuzumab Duocarmazine (SYD985)[1,2]



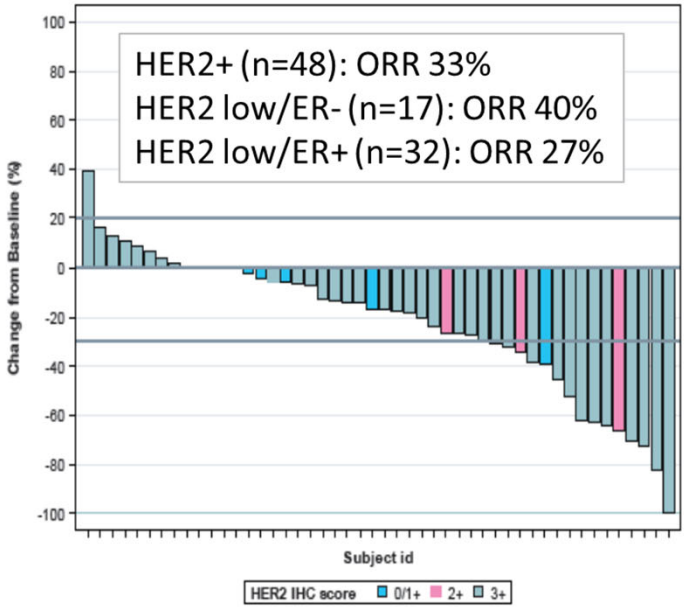
- HER2-targeting ADC[1]
- Duocarmycins are DNA-alkylating agents composed of a DNA-alkylating and a DNA-binding moiety[2]

1. Banerji U et al. *Lancet Oncol*. 2019;20(8):1124-1135; 2. Rinnerthaler G et al. *Int J Mol Sci*. 2019;20(5):1115.

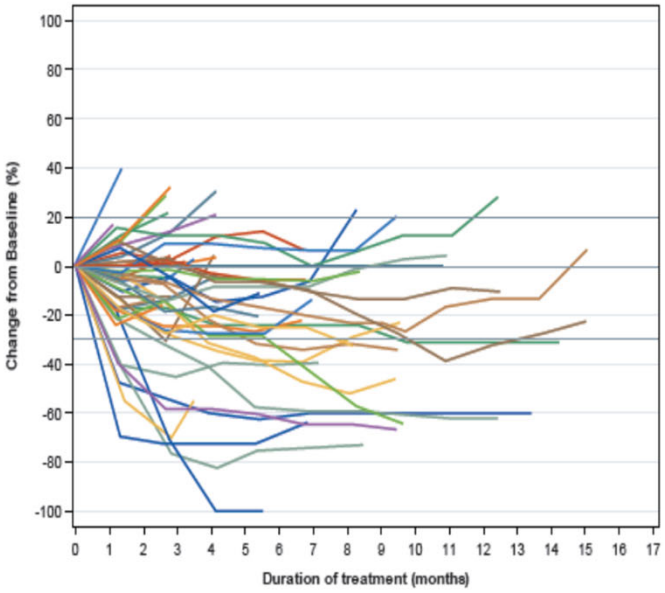
Trastuzumab-Duocarmazine
SYD-985

Clinical Trial Design
(Phase I)

Best percentage change from baseline in target lesions



Percentage change from baseline in target lesions over time



Saura C, et al. ASCO 2018

New Antibody-Drug Conjugates Trastuzumab-Duocarmazine

Clinical Trial Design (TULIP)

Patients with HER2+, unresectable, locally advanced and/or metastatic BC; progression on or after ≥ 2 HER2-targeted regimens or after T-DM1; ECOG PS 0-2 (Planned N = 345)

- Trastuzumab Duocarmazine Q3W (planned n = 230)
- Physician's Choice: Lapatinib/Capecitabine, Trastuzumab/Capecitabine, Trastuzumab/Vinorelbine, Trastuzumab/Eribulin (planned n = 115)

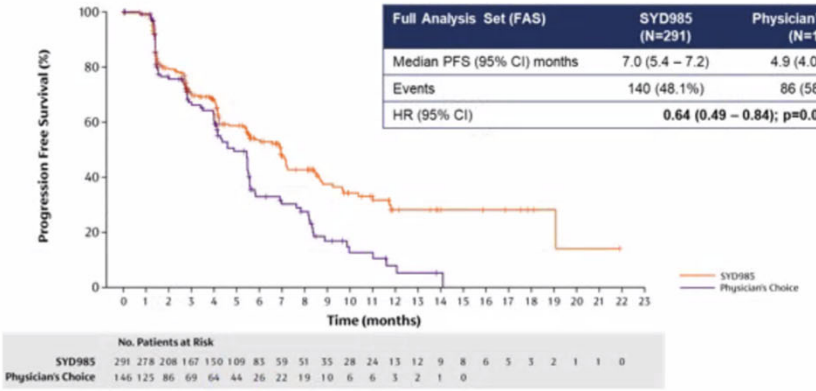
ORR

Number of patients with	SYD985 (N=291)	Physician's choice (N=146)
Measurable disease at baseline	252 (86.6%)	122 (83.6%)
Overall Response Rate# (PR or CR)	70 (27.8%)	36 (29.5%)
Reduction Target lesion measurement#	177 (70.2%)	71 (58.2%)
Clinical Benefit Rate	112 (38.5%)	47 (32.2%)

#pts with measurable disease used as denominator

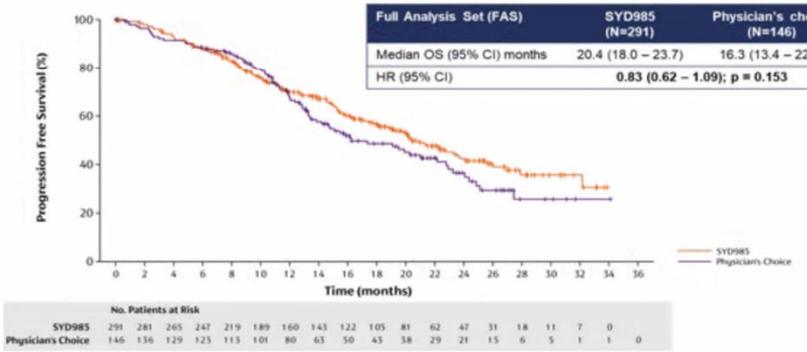
PFS

Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	0.64 (0.49 – 0.84); p=0.002	



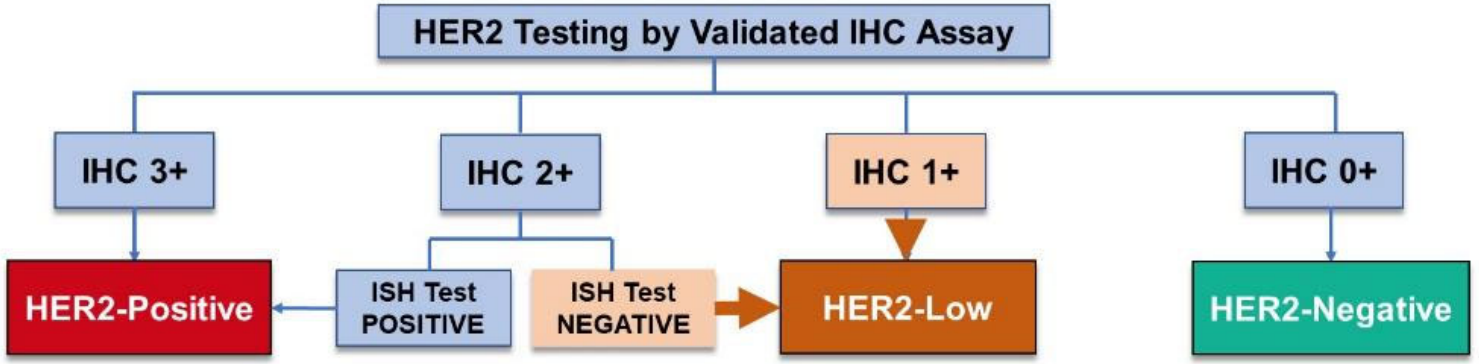
OS

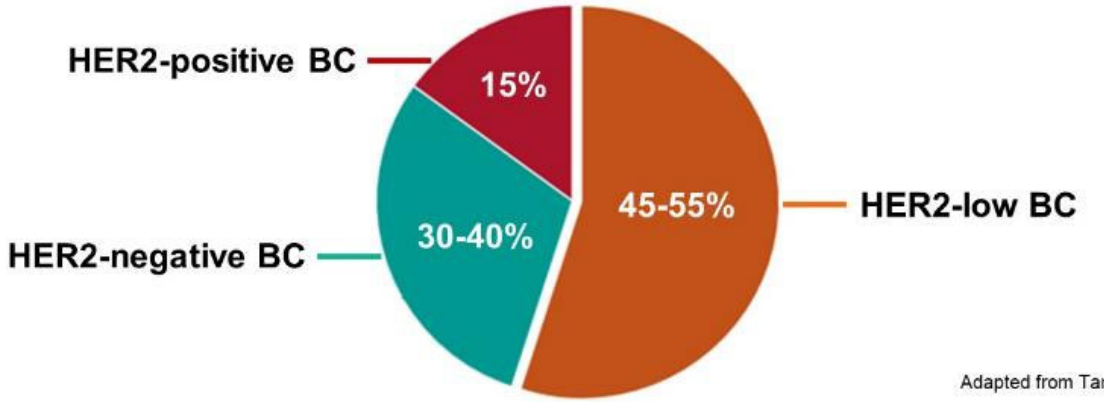
Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median OS (95% CI) months	20.4 (18.0 – 23.7)	16.3 (13.4 – 22.8)
HR (95% CI)	0.83 (0.62 – 1.09); p = 0.153	



Saura C, et al. ESMO 2021

Proposal of an algorithm for defining HER2-low BC





Adapted from Tarantino et al. J Clin Oncol. 2020 38(17)

Role for HER2-directed agents in HER2-low breast cancer? NSABP B-47

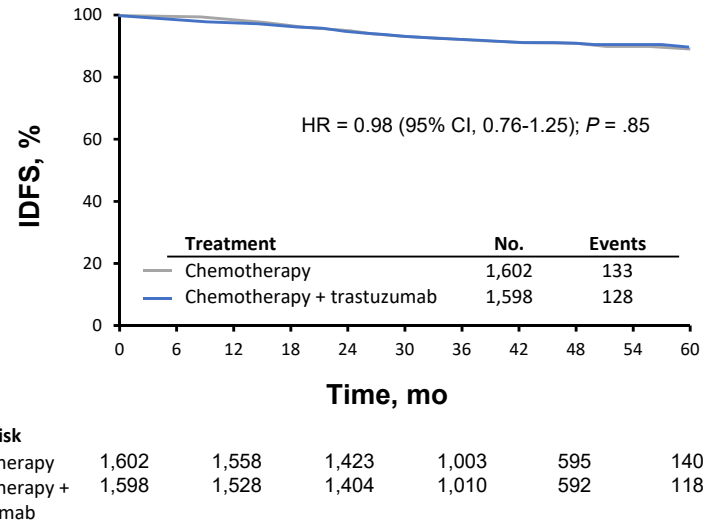
A phase 3 trial was conducted to understand if adjuvant trastuzumab was beneficial for HER2-low patients

- Node-positive or high-risk node-negative breast cancer
- IHC 1+, 2+ and FISH negative

R

Docetaxel/cyclophosphamide
or
AC → weekly paclitaxel (WP)

TC + trastuzumab → trastuzumab x 1 y
or
AC → **weekly paclitaxel + trastuzumab → trastuzumab x 1 y**



No. at Risk						
Chemotherapy	1,602	1,558	1,423	1,003	595	140
Chemotherapy + trastuzumab	1,598	1,528	1,404	1,010	592	118

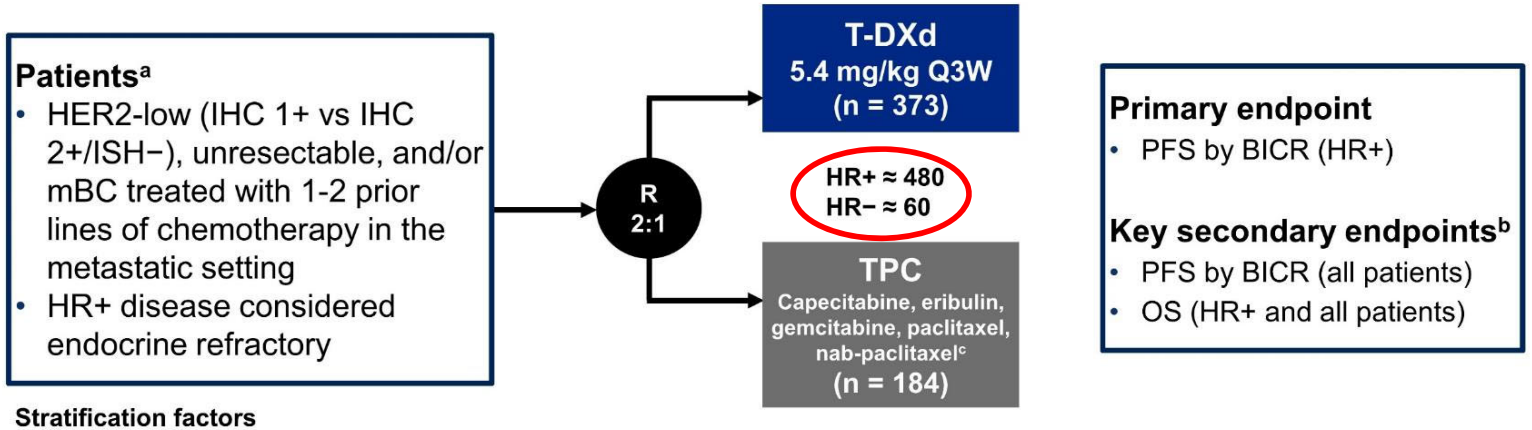
No benefit of adjuvant trastuzumab for HER2-low patients

Fehrenbacher L et al. *J Clin Oncol*. 2020;38:444-453.

DESTINY-Breast04

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

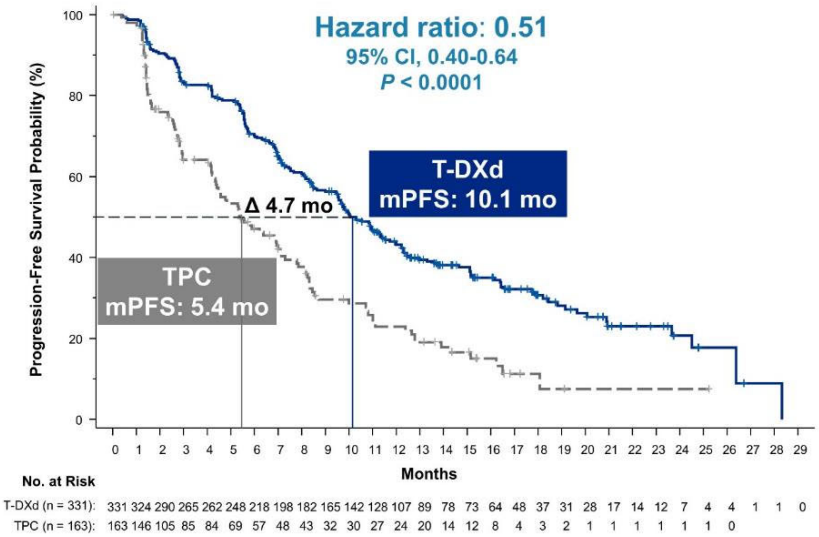
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

PRESENTED BY:
Shanu Modi, MD

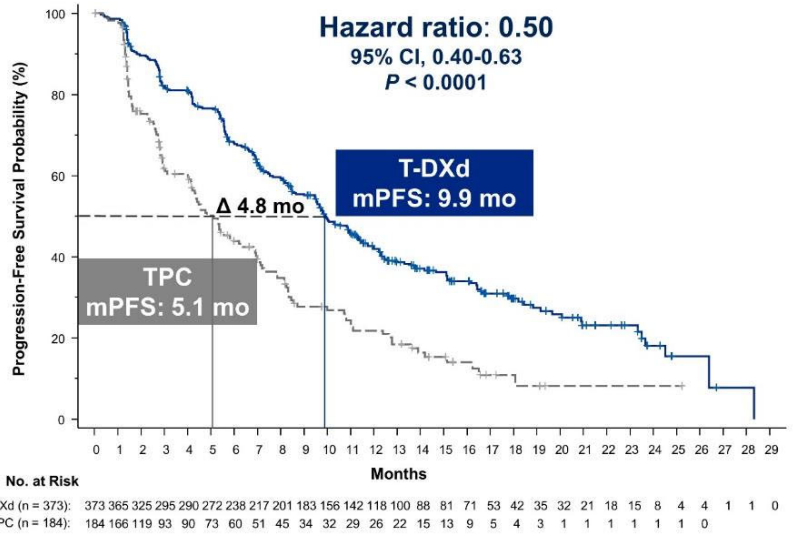
DESTINY-Breast04

PFS in HR+ and All Patients

Hormone receptor–positive



All patients



PFS by blinded independent central review.

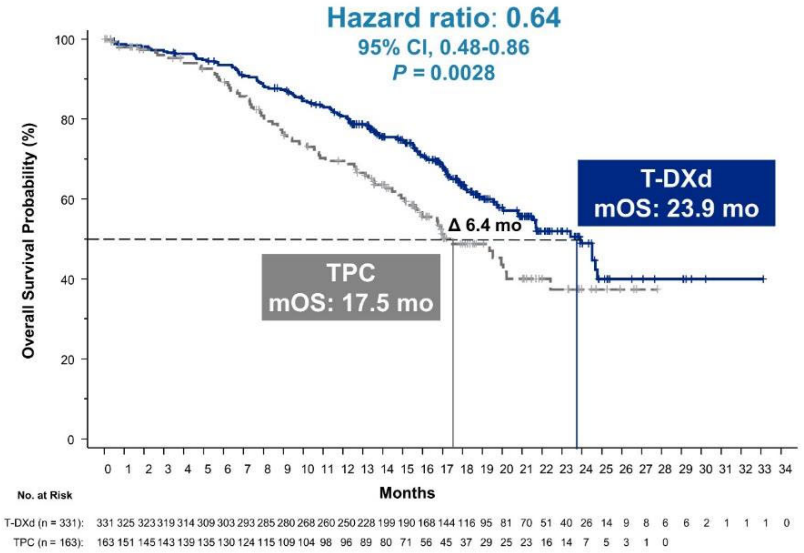
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PRESENTED BY:
Shanu Modi, MD

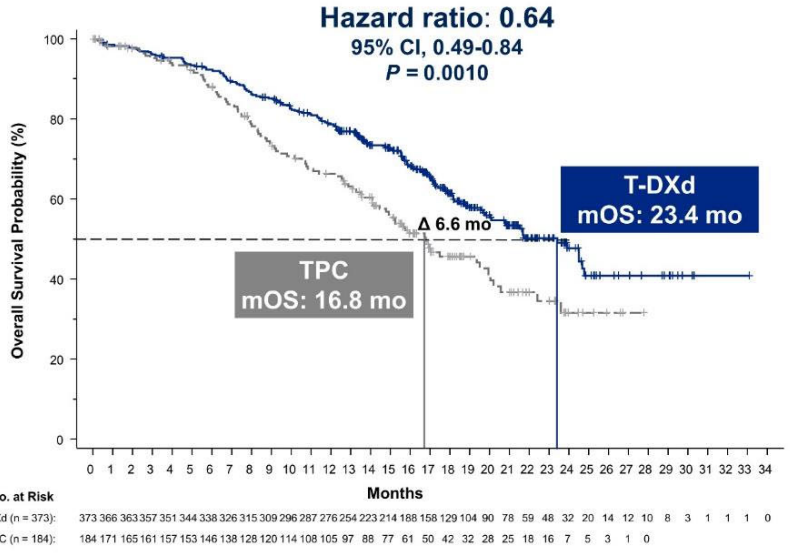
DESTINY-Breast04

OS in HR+ and All Patients

Hormone receptor–positive



All patients



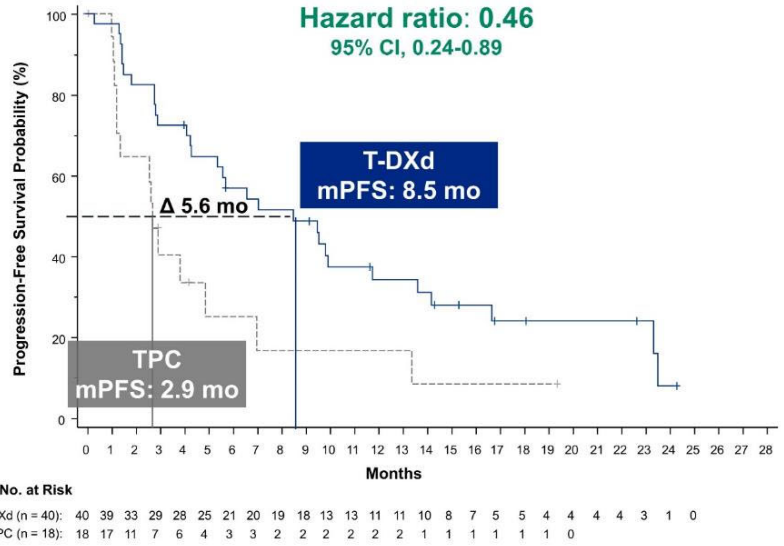
HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PRESENTED BY:
Shanu Modi, MD

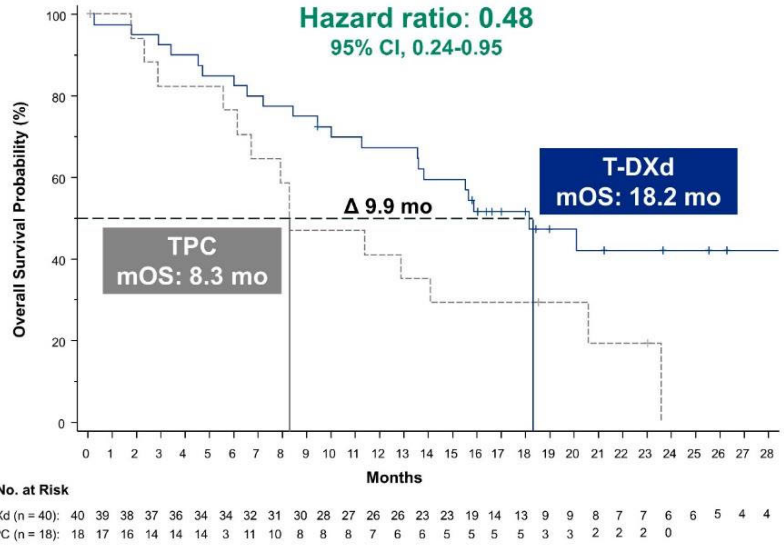
DESTINY-Breast04

PFS and OS in HR− (Exploratory Endpoints)

PFS



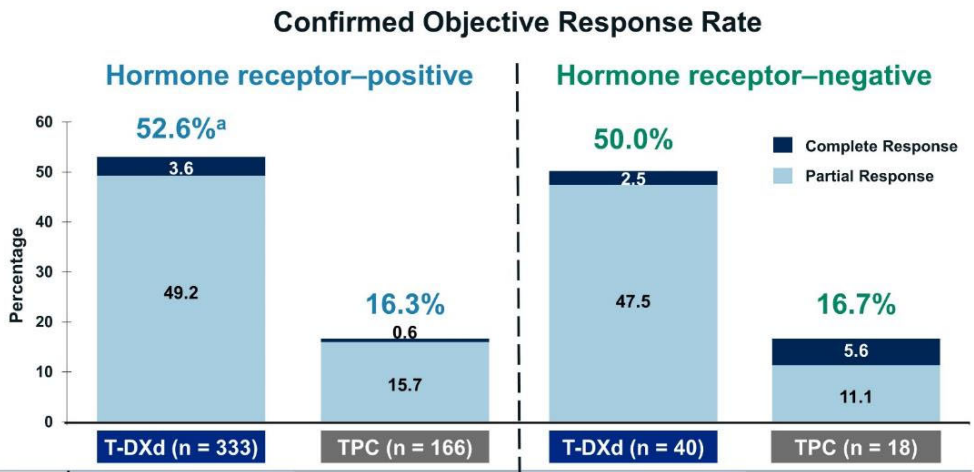
OS



HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

DESTINY-Breast04

Confirmed ORR



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

PRESENTED BY:
Shanu Modi, MD

Next Challenge: How LOW can we go?

DAISY

	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n / N [95%CI]	86 / 177 (48.6%) [41.0; 56.2]	48 / 68 (70.6%) [58.3; 81.0]	27 / 72 (37.5%) [26.4; 49.7]	11 / 37 (29.7%) [15.9; 47.0]
Median DOR (months) [95%CI]	8.5 [6.5; 9.8]	9.7 [6.8; 13]	7.6 [4.2; 9.2]	6.8 [2.8; Not reached]
Median PFS (months) [95%CI]	7.0 [6.0; 8.7]	11.1 [8.5; 14.4]	6.7 [4.4; 8.3]	4.2 [2.0; 5.7]

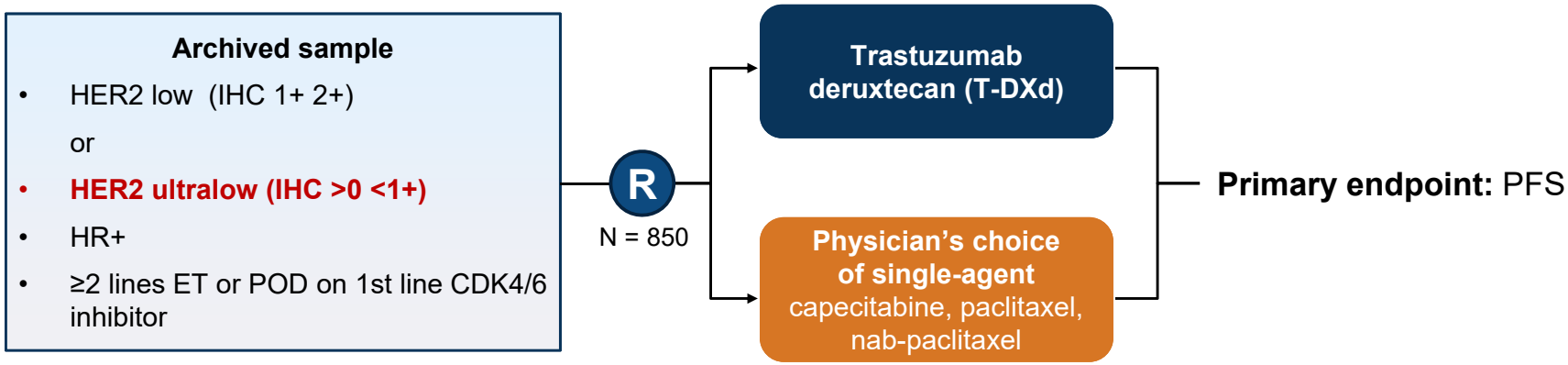
IHC 3+ **IHC 1+ or 2+** **IHC 0**

Decreasing ORR by degree of HER2 expression

Dieras V et al, SABCS 2021

Potential Future Challenge: HER2 "Ultralow"

- DESTINY-Breast06 phase 3 includes IHC 0 with "ultralow" expression and may expand the population of patients deriving benefit from T-DXd



- **Key differences with DESTINY-Breast04:** includes IHC 0+ ("ultralow"), larger (N = 850), restricted to HR+ disease, and includes chemo-naïve patients

https://clinicaltrials.gov/ct2/show/NCT04494425.

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NCCN Member Institutions

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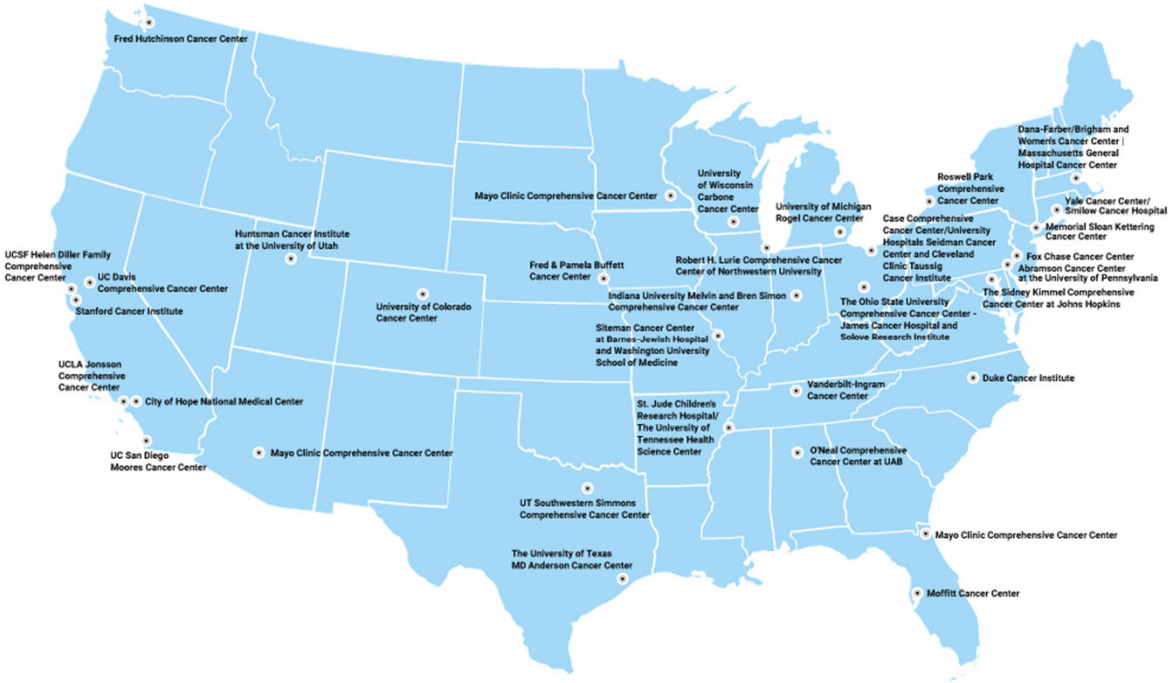
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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