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Metastatic breast cancer : new diagnostic and therapeutic approaches

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Learning objectives

- To review the appropriate diagnostic workup for metastatic breast cancer (MBC)
- To review current guidelines for the treatment and monitoring of metastatic breast cancer
- To understand recent key developments in drugs to treat MBC

Lecture structure

- Case based
- NCCN-guideline focused
- Emphasis on standard therapies

Locally recurrent disease: Case 1

60 year-old patient with a history of stage IIIA ER/PR+, HER2- breast cancer treated 6 years prior with neoadjuvant anthracycline-based chemotherapy, lumpectomy with sentinel lymph node biopsy (SLNB), radiation and 5 years of an aromatase inhibitor, presents with an expanding mass near her lumpectomy scar. Biopsy demonstrates invasive ductal carcinoma with similar histology to her prior tumor. Your next step is:

A) Mastectomy with SLNB
B) Mastectomy with axillary lymph node dissection (ALND)
C) Chemotherapy
D) A and C
E) B and C

Locally recurrent disease: Case 1

- Answer: B Mastectomy with ALND
  - –Actual real first step: Probably restaging
  - –Patients with prior mastectomy should undergo surgical resection (if possible) and radiation to the chest wall and supraclavicular area (if the chest wall was not previously irradiated). Benefit of repeat SLN biopsy after mastectomy is unknown, but not encouraged.
  - –Patients with prior breast-conserving surgery and radiation therapy with prior SLNB: NCCN panel consensus recommendation is mastectomy and a level I/II axillary dissection.

Locally recurrent disease: A case for chemotherapy?

- CALOR trial (Lancet 2014): Studied effect of chemotherapy after complete resection in patients with isolated locoregional recurrence
- Adjuvant chemotherapy improved DFS and OS. Five-year OS 88% vs. 76%, *P* .024 in chemo vs non-chemo group.
- Benefit of adjuvant chemotherapy was only significant in hormone-receptor negative disease: DFS = 67% versus 35% for ER negative disease; DFS = 70% versus 69% in ER-positive disease, (HR, 0.94; 95% CI, 0.47–1.89).

Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol 2014;15:156-163

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Efficacy of Chemotherapy for ER-Negative and ER-Positive Isolated Locoregional Recurrence of Breast Cancer: Final Analysis of the CALOR Trial

Irene L. Wapnir, Karen N. Price, Stewart J. Anderson, André Robidoux, Miguel Martín, Johan W.R. Nortier, Alexander H.G. Paterson, Mothaffar F. Rimawi, István Láng, José Manuel Baena-Cañada, Beat Thürlimann, Eleftherios P. Mamounas, Charles E. Geyer Jr, Shari Gelber, Alan S. Coates, Richard D. Gelber, Priya Rastogi, Meredith M. Regan, Norman Wolmark, and Stefan Aebi, on behalf of the International Breast Cancer Study Group, NRG Oncology, GEICAM Spanish Breast Cancer Group, BOOG Dutch Breast Cancer Trialists' Group, and Breast International Group

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ABSTRACT

Purpose
Isolated locoregional recurrence (ILRR) predicts a high risk of developing breast cancer distant metastases and death. The Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial investigated the effectiveness of chemotherapy (CT) after local therapy for ILRR. A report at 5 years of median follow-up showed significant benefit of CT for estrogen receptor (ER)–negative ILRR, but additional follow-up was required in ER-positive ILRR.

Patients and Methods
CALOR was an open-label, randomized trial for patients with completely excised ILRR after unilateral breast cancer. Eligible patients were randomly assigned to receive CT or no CT and stratified by prior CT, hormone receptor status, and location of ILRR. Patients with hormone receptor–positive ILRR received adjuvant endocrine therapy. Radiation therapy was mandated for patients with microscopically involved margins, and anti–human epidermal growth factor receptor 2 therapy was optional. End points were disease-free survival (DFS), overall survival, and breast cancer-free interval.

Results
From August 2003 to January 2010, 162 patients were enrolled: 58 with ER-negative and 104 with ER-positive ILRR. At 9 years of median follow-up, 27 DFS events were observed in the ER-negative group and 40 in the ER-positive group. The hazard ratios (HR) of a DFS event were 0.29 (95% CI, 0.13 to 0.67; 10-year DFS, 70% *v* 34%, CT *v* no CT, respectively) in patients with ER-negative ILRR and 1.07 (95% CI, 0.57 to 2.00; 10-year DFS, 50% *v* 59%, respectively) in patients with ER-positive ILRR ($P_{interaction}$ = .013). HRs were 0.29 (95% CI, 0.13 to 0.67) and 0.94 (95% CI, 0.47 to 1.85), respectively, for breast cancer-free interval ($P_{interaction}$ = .034) and 0.48 (95% CI, 0.19 to 1.20) and 0.70 (95% CI, 0.32 to 1.55), respectively, for overall survival ($P_{interaction}$ = .53). Results for the three end points were consistent in multivariable analyses adjusting for location of ILRR, prior CT, and interval from primary surgery.

Conclusion
The final analysis of CALOR confirms that CT benefits patients with resected ER-negative ILRR and does not support the use of CT for ER-positive ILRR.

J Clin Oncol 36:1073-1079. © 2018 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying Editorial on page 1058

Data Supplements
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INTRODUCTION

The increased use of adjuvant radiation and systemic therapies and the improved efficacy of such therapies in the past two decades have resulted in a lower incidence of locoregional recurrence of breast cancer.[1-5] However, after an isolated locoregional recurrence (ILRR) event of breast cancer, the risk of distant metastases and death is high.[6-9] The Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial was designed as a prospective randomized study to determine the effectiveness of adjuvant chemotherapy (CT) after surgical excision of ILRR. Previously, we reported the results at a median follow-up of 5 years, which showed significant benefit of CT for estrogen

Diagnosis and workup: Case 2

A 56 yo postmenopausal woman presents with a self-detected R breast lump. Diagnostic mammogram demonstrates a 4 cm R breast mass at 3:00, N+8. MRI shows a 5.1 cm unifocal mass, and three suspicious-appearing axillary lymph nodes. Biopsy reveals grade 2 invasive lobular carcinoma, ER+ (95%), PR+ (75%), HER2 1+. She inquires about next steps. You advise:

A) Neoadjuvant chemotherapy with ddAC/T
B) Surgical resection with SLNB
C) PET scan
D) Biopsy to evaluate extent of disease
E) CT C/A/P and bone scan

Diagnosis and workup: Staging

- Answer: E.
  - –NCCN guidelines: "For patients presenting with disease confined to the breast (stage I to II) the NCCN Panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients who present with locally advanced (T3 N1-3 M0) disease and in those with signs or symptoms suspicious for metastatic disease."

Diagnosis and workup: Imaging

- Why not a PET?
  - –The non-diagnostic CT scans used for PET under-evaluate the lungs and the liver compared with contrast-enhanced diagnostic CT scans.
  - –FDG PET/CT is optional, may be most helpful when other imaging is equivocal or suspicious.

Diagnosis and workup: Case 2, con't

The patient undergoes CT C/A/P and bone scan, which reveal multiple lesions in liver, the largest measuring 2 cm, and diffuse metastases to the spine and axial skeleton. The patient endorses lower back pain x 2 months which you suspect corresponds to an L3 lesion. She inquires about next steps. You advise:

A) Initiate treatment with a CDK 4/6 inhibitor and endocrine therapy
B) MRI spine w/ referral to radiation oncology for RT to L3
C) Liver biopsy
D) L3 biopsy

Diagnosis and workup: Biopsy

- Answer: C, Liver biopsy
  - –Metastatic disease should be biopsied at first presentation or at first recurrence in order to confirm the diagnosis and determine tumor histology and molecular profile.
  - –Soft tissue tumor biopsy preferred over bone sites as demineralization procedures can degrade proteins and DNA needed for IHC, FISH and molecular assays. For clinical (non-board exam) purposes, request EDTA decalcification if possible to avoid this issue – this process is somewhat slower, but preserves proteins and nucleotides.

Diagnosis and workup: Markers

- IHC and FISH: ER, PR and HER2 status (primary and metastatic sites can be discordant), PDL1.
- Molecular markers for MBC with clinical significance (not standard or recommended for early-stage disease): PIK3CA, TMB, ERBB2. Rare but useful if found: MSI (rare), NTRK, high tumor mutational burden (TMB). Possible future significance: FGFR2, AKT, ATM, others.
- Genetic testing: Germline BRCA1/2 mutations should be assessed in all patients with recurrent or metastatic breast cancer as positive results have implications for therapy

Biomarkers and targeted therapies

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[c]	Category 1	Preferred second- or subsequent-line therapy
TNBC	PD-L1 expression (using 22C3 antibody) Threshold for positivity combined positive score ≥10	IHC	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[d]	Category 1	Preferred first-line therapy[h]
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e] Entrectinib[e]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[d,f] Dostarlimab-gxly[g]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[d,f]	Category 2A	

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Treatment: Case 2, con't

This patient's biopsy of her largest liver mass returns with the same histology as index tumor (ER/PR+, HER2-). Molecular analysis reveals a PIK3CA mutation. You advise:

A) Tamoxifen
B) CDK 4/6 inhibition plus endocrine therapy
C) Alpelisib plus fulvestrant
D) Capecitabine

Treatment: First line therapy for HR+ disease

- Answer: B, CDK4/6 inhibition plus endocrine therapy.
  - –Aromatase inhibitor in combination with CDK4/6 inhibition is a preferred first-line treatment.
  - –Trials of all three medications in this class have demonstrated improved PFS over AI alone: MONALEESA-2 and -7 (ribociclib), PALOMA-2 (palbociclib), MONARCH-3 (abemaciclib).
  - –Only MONALEESA 7 looked at premenopausal patients, but all these agents are given to young patients along with ovarian suppression or BSO.

Recommended CDK4/6 Inhibitors in 1L HR+ HER2- MBC

Parameter*	PALOMA-2[1,2]	MONALESSA-2[3,4]	MONALEESA-7[5,6]	RIGHT Choice[7]	MONARCH 3[8]
N	666	668	672	222	493
Treatment arm	Letrozole ± palbociclib	Letrozole ± ribociclib	Tamoxifen, anastrozole, or letrozole ± ribociclib	Ribociclib + anastrozole + goserelin or letrozole vs Inv choice of CT	Anastrozole or letrozole ± abemaciclib
Patient population	Postmenopausal adv BC; no previous systemic tx†	Postmenopausal adv BC with recurrent or MBC; no previous systemic tx†	Pre/perimenopausal advanced BC; no previous ET for adv BC	Adv or metastatic BC; with aggressive disease§ no previous systemic tx	Locally advanced or MBC; postmenopausal; no previous systemic tx
Median PFS, mo (HR; *P* value)	27.6 vs 14.5 (0.56; .0001)[1]	25.3 vs 16.0 (0.57; .0001)[3]	23.8 vs 13.0 (0.55; .0001)[5]	24.0 vs 12.3 (0.65; .00065)	29.0 vs 14.8 (0.518; .0001)
Median OS, mo (HR; *P* value)	53.9 vs 51.2 (0.96; .3378)[2]	63.9 vs 51.4 (0.76; .008)[4]	NE vs 40.9 (0.71; .0097)[6]	--	67.1 vs 54.5 (0.754; .0301)
Common grade ≥3 AEs (%)	Neutropenia (69.1), WBC decrease (26.0), anemia (7.0)	Neutropenia (52.0), hypertension (15.6), WBC decrease (13.8)	Neutropenia (64.0), WBC decrease (16.1), hepatobiliary (11.0)	Neutropenia (58.0), WBC decrease (23.2), and anemia (5.4)	Neutropenia (27), diarrhea (9.8), and anemia (8.9)

Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174:719. 2. Finn R, et al. ASCO 2022. Abstr LBA1003. 3. Hortobagyi GN, et al. *Ann Oncol*. 2018;29;1541. 4. Hortobagyi GN, et al. *NEJM*. 2022;386;942. 5. Tripathy D, et al. *Lancet Oncol*. 2018;19;904. 6. Im S, et al. *NEJM*. 2019;381;307. 7. Lu Y-S, et al. SABCS 2022. Abstr GS1-10. 8. Goetz M, et al. ESMO 2022. Abstr LBA15.

Treatment for HR+ MBC: CDK4/6 inhibitors

- All CDK 4/6 inhibitors exhibit hematologic toxicities (neutropenia, leukopenia), GI toxicities, elevated LFTs, increased risk of pulmonary embolism
- Ribociclib: QTc prolongation, administration requires cardiac monitoring
- Abemaciclib: Higher incidence of all-grade and grade 3/4 gastrointestinal toxicities, seems to have some blood/brain barrier penetration, is given continuously, and can be given as monotherapy.

Sammons SL et al, Curr Cancer Drug Targets. 2017 Sep; 17(7): 637–649.

Treatment for HR+ MBC: Other first-line therapies

- Fulvestrant monotherapy. (Improved time to progression was seen with fulvestrant compared to anastrazole, FIRST study)
- Fulvestrant + AI (mixed trial results, FACT and SoFEA)
- Fulvestrant + CDK4/6 inhibitor
- Monotherapy with endocrine agents

Ellis MJ, Llombart-Cussac A, Feltl D, et al. J Clin Oncol 2015;33:3781-3787.
Bergh J, Jonsson PE, Lidbrink EK, et al. J Clin Oncol. 2012;30:1919-1925
Johnston SR, Kilburn LS, Ellis P, et al. Lancet Oncol 2013;14:989-998.

Treatment: Case 2, con't

Nine months later, scans reveal that the patient's tumor has progressed, demonstrating enlarging mediastinal nodes and new bone metastases. Depending on the the patient's PS and tumor characteristics, as a next line of therapy you could choose:

A) Fulvestrant monotherapy

B) Exemestane + everolimus

C) Targeted therapy

D) Any of the above

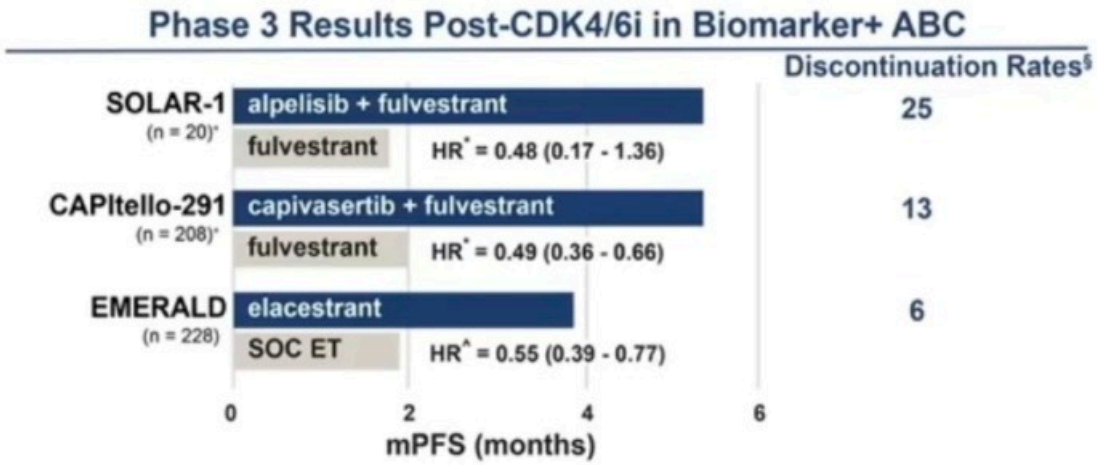
Treatment: Case 2, con't

- Answer: D, any of the above. Acceptable second line regimens for HR+ MBC include:
  - –Fulvestrant monotherapy
  - –Fulvestrant + CDK 4/6 inhibitor
  - –Exemestane + everolimus
  - –Targeted therapy when appropriate. In this patient, many would choose a targeted therapy given her PIK3CA mutation.

Second line therapy for HR+ MBC: Targeted agents

- *PIK3CA* mutations: ~40% of patients with hormone-receptor positive, HER2-negative breast cancer
- PFS=11.0 months in the alpelisib–fulvestrant group, vs. 5.7 months in the placebo–fulvestrant group
- FDA approval: May 24, 2019, along with approval for companion diagnostic
- For ER/PR+ patients with advanced breast cancer following progression on or after endocrine-based treatment
- Common SEs: Rash, hyperglycemia, diarrhea

Target-Driven Therapy Beyond CDK4/6 Inhibitors



*Post CDK4/6i Subgroup, ^Investigator PFS, ^BICR PFS, §ITT population

Juric D, et al. Proceedings of SABCS 2019 79(4) GS3-08; Oliveria M, et al. *Ann Oncol* 8(1) 2023; Turner N, *N Engl J Med* 388(22) 2058-2070, Bidard F, et al. 2022 *J Clin Oncol* 40(28) 3246-32568

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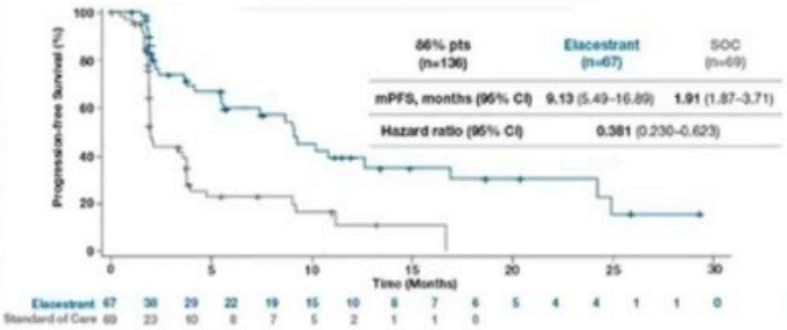
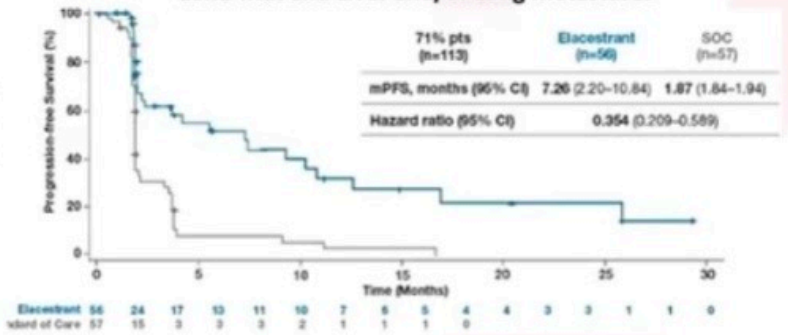
EMERALD PFS Subanalyses: Elacestrant vs SOC ET

PFS in Patients with ≥12 Months Prior CDK4/6i with *ESR1*-mut and Bone Metastases



PFS in Patients with ≥12 Months Prior CDK4/6i with *ESR1*-mut and Liver and/or Lung Metastases



PFS Across All Relevant Subgroups with *ESR1*-mut and ≥12 Months Prior CDK4/6i with

Patients	% (n)	Median PFS, months (95% CI) Elacestrant	SOC	HR (95% CI)
All *ESR1*-mut patients[a]	100 (159)	8.61 (4.14–10.84)	1.91 (1.87–3.68)	0.410 (0.262–0.634)
ESR1-mut and bone metastases[a]	86 (136)	9.13 (5.49–16.89)	1.91 (1.84–3.71)	0.381 (0.230–0.623)
ESR1-mut and liver and/or lung metastases[b]	71 (113)	7.26 (2.20–10.84)	1.87 (1.87–1.94)	0.354 (0.209–0.589)
ESR1-mut and *PIK3CA*-mut[c]	39 (62)	5.45 (2.14–10.84)	1.94 (1.84–3.94)	0.423 (0.176–0.941)
ESR1-mut and HER2-low expression[d]	48 (77)	9.03 (5.49–16.89)	1.87 (1.84–3.75)	0.301 (0.142–0.604)
ESR1-mut and *TP53*-mut	38 (61)	8.61 (3.65–24.25)	1.87 (1.84–3.52)	0.300 (0.132–0.643)

[a]Bone and others 86% of patients; [b]Liver and others 55% of patients / Lung and others 26% of patients; [c]Includes E545K, H1047R, E542K amongst others; [d]HER2 IHC 1+, and 2+ with no ISH amplification. Data not available for all patients

Bardia A, et al. SABCS 2023. Abstract PS17-02.

New #ASCO24

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

Abemaciclib + Fulvestrant

Placebo + Fulvestrant

Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

- Enrolled March 2022 to June 2023 across 96 centers in 16 countries
- Scans every 8 weeks for the first 12 months, then every 12 weeks
- Primary outcome targeted 251 events; interim analysis planned at ~70% of events
- Assuming a hazard ratio (HR) of 0.70, ~80% power to detect abemaciclib superiority, with a cumulative 2-sided type I error of 0.05
- Biomarker ctDNA analyzed by GuardantINFINITY assay

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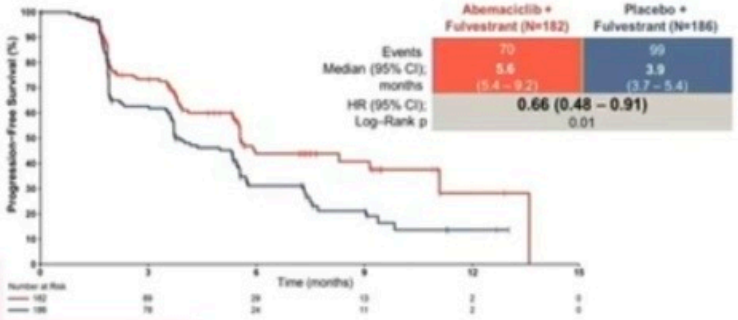
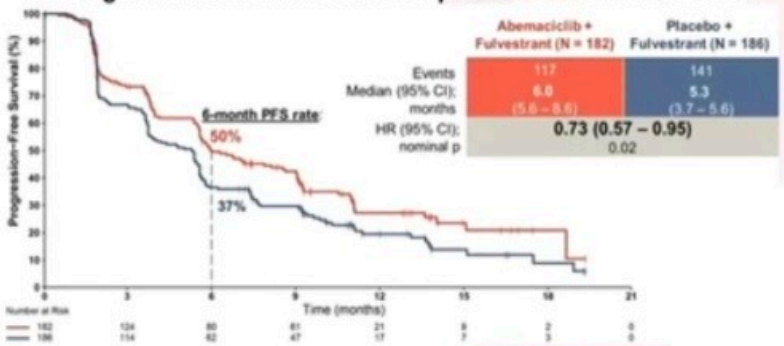
Kalinsky K, et al. ASCO 2024. Abstract LBA1001

New #ASCO24

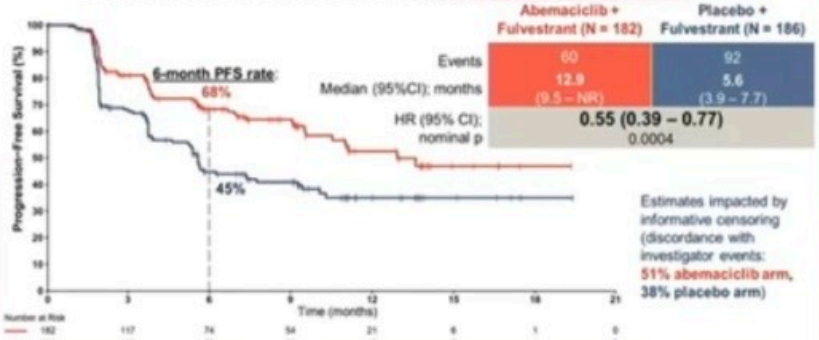
Investigator Assessed PFS



Investigator assessed 6-month PFS improved 27% from 37% to 50%



BICR-Assessed 6 Month PFS improved 23% from 45% to 68%

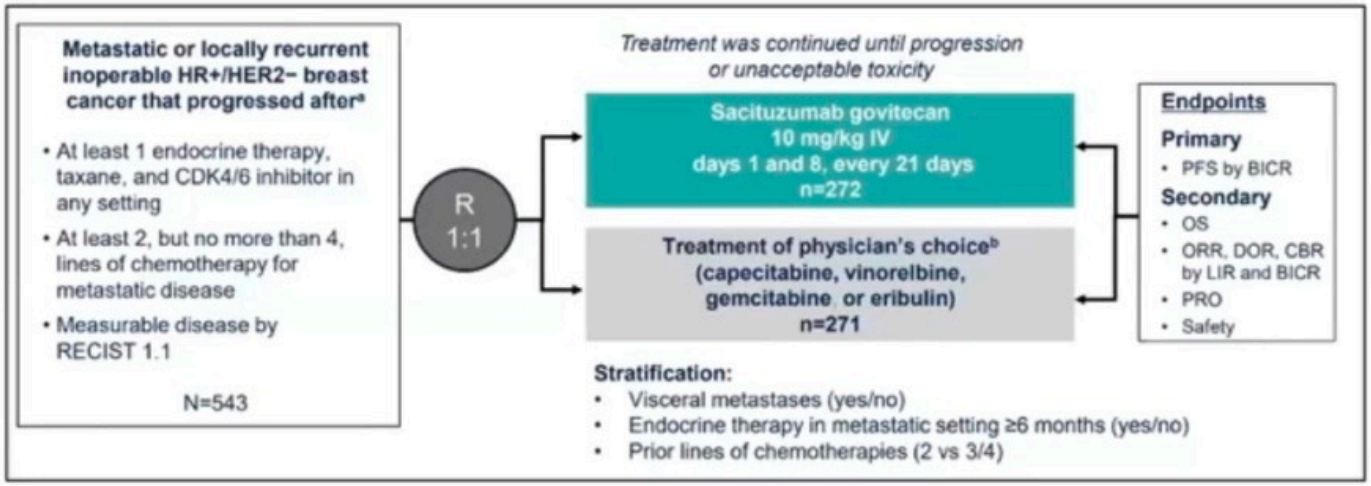


Estimates impacted by informative censoring (discordance with investigator events: 51% abemaciclib arm, 38% placebo arm)

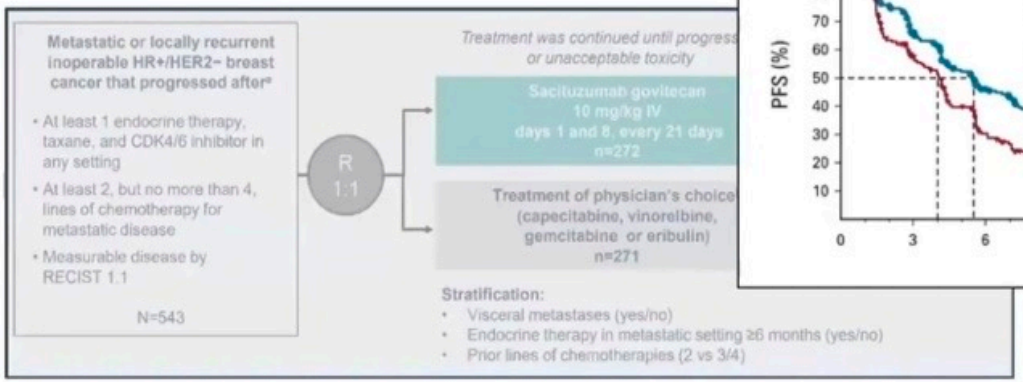
Kalinsky K, et al. ASCO 2024. Abstract LBA1001

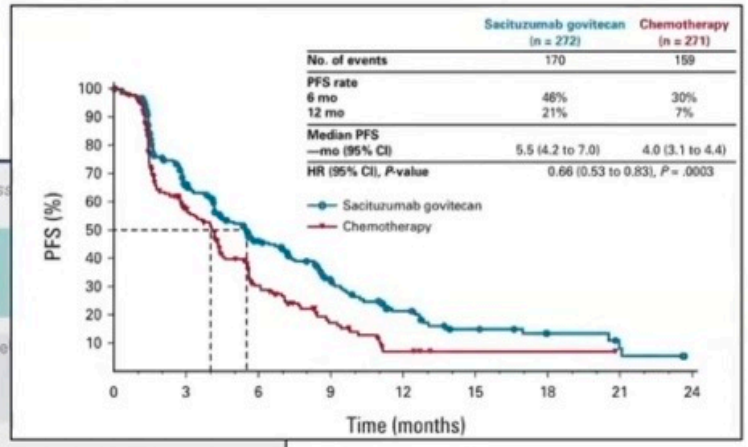
HR-Positive and HER2-Negative with Visceral Crisis† or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	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)

Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer



Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer





	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46%	30%
12 mo	21%	7%
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	

Sacituzumab Govitecan in Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

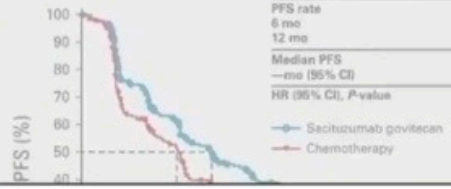
Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543

Treatment was continued until progress or unacceptable toxicity

Sacituzumab govitecan



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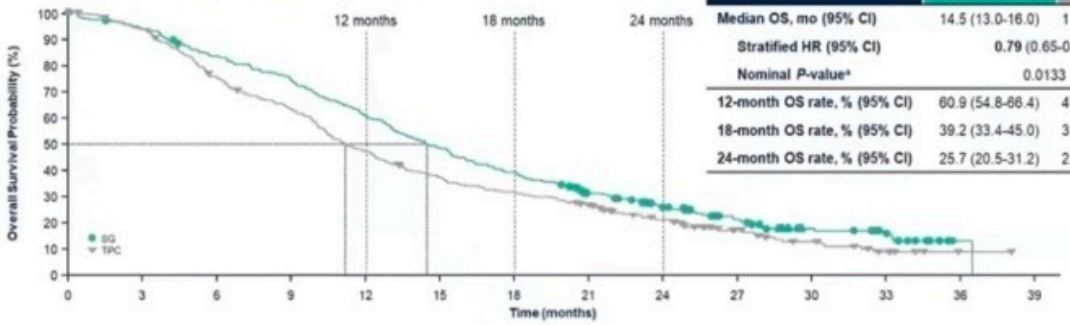
Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	0.79 (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

ET + CDKi

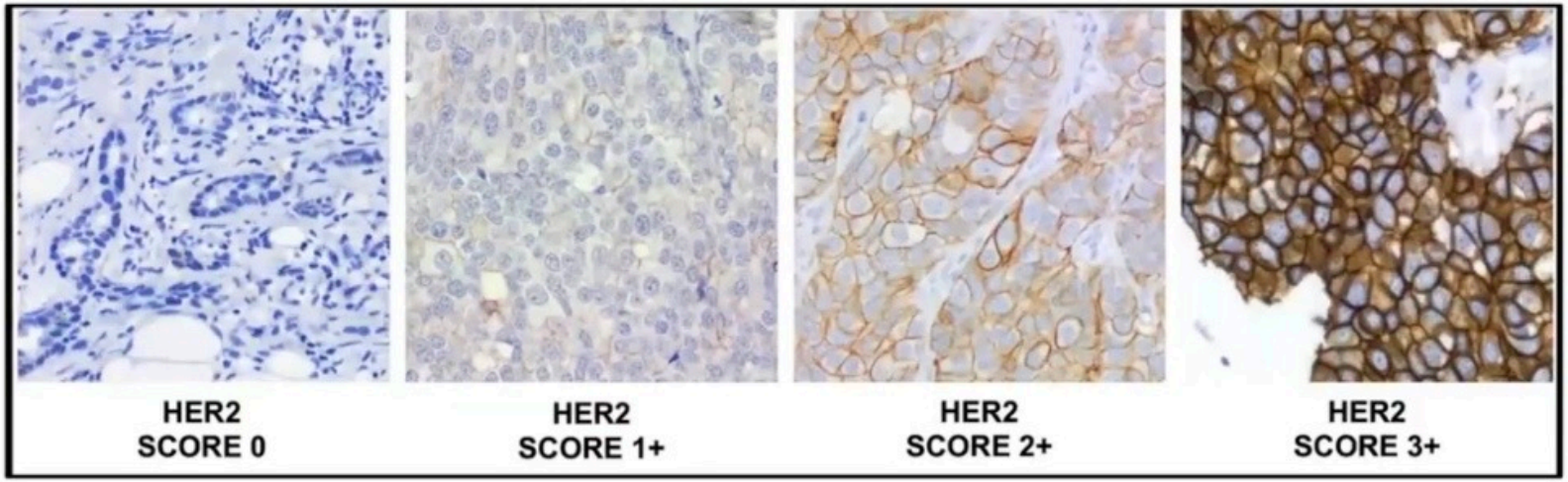
Scenario	Potential 2nd-line
*ESR1*mut, PFS 1st-line ≥12 months, non-high risk	elacestrant
*PIK3CA*mut	alpelisib + ET*
*BRCA*mut	PARPi
*ESR1*wt, *PIK3CA*wt, *BRCA*wt	everolimus + ET* or ribociclib + ET* (in case of prolonged CDKi benefit 1st-line)
HER2 low, high-risk, endocrine resistance	T-DXd
HER2 0 neg., high-risk, endocrine resistance	chemotherapy or SG

Alternative ET* +/- targeted therapy or chemotherapy or ADC depending upon prior therapy, risk profile and disease biology

*depending upon prior therapy

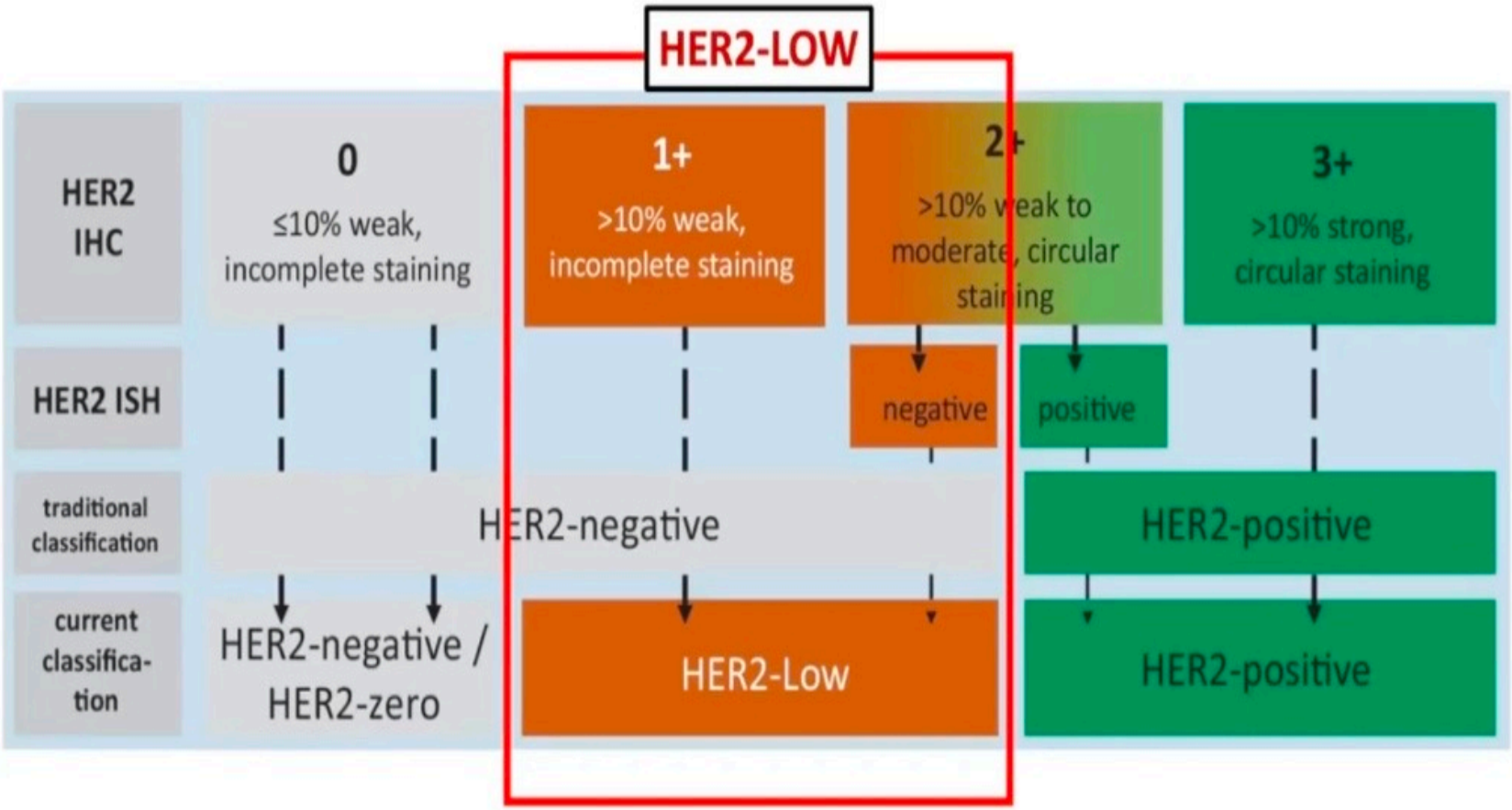
Need for novel quantitative assays

Difference between HER2 zero and 1+ by IHC is subtle.



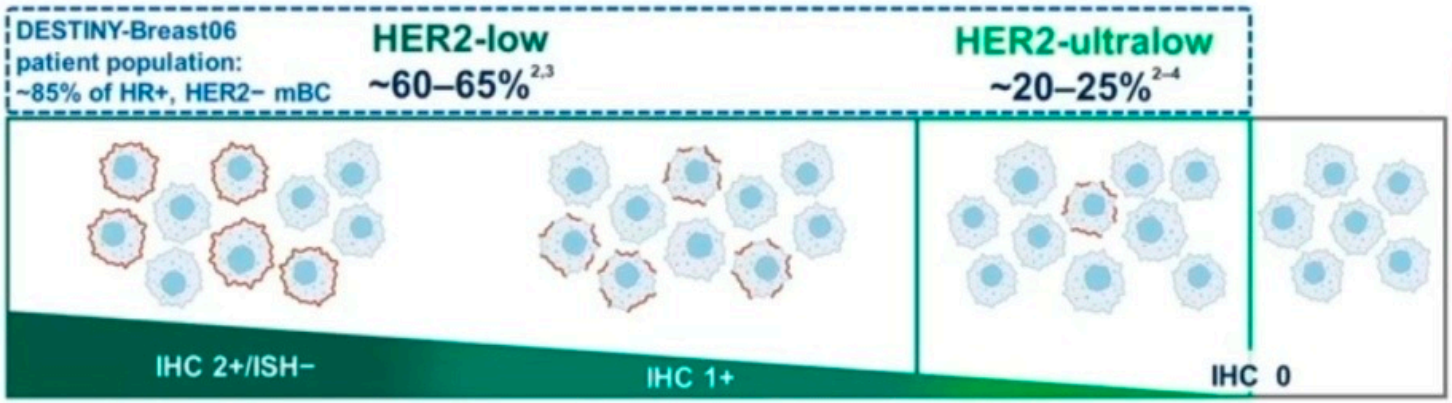
Marchio et al. Seminars in Cancer Biology 2021

Definition of Her2-low breast cancer



Curigliano G, et al. ASCO 2024. Abstract LBA1000.

HER2 Low, and now HER2 "*Ultralow*"

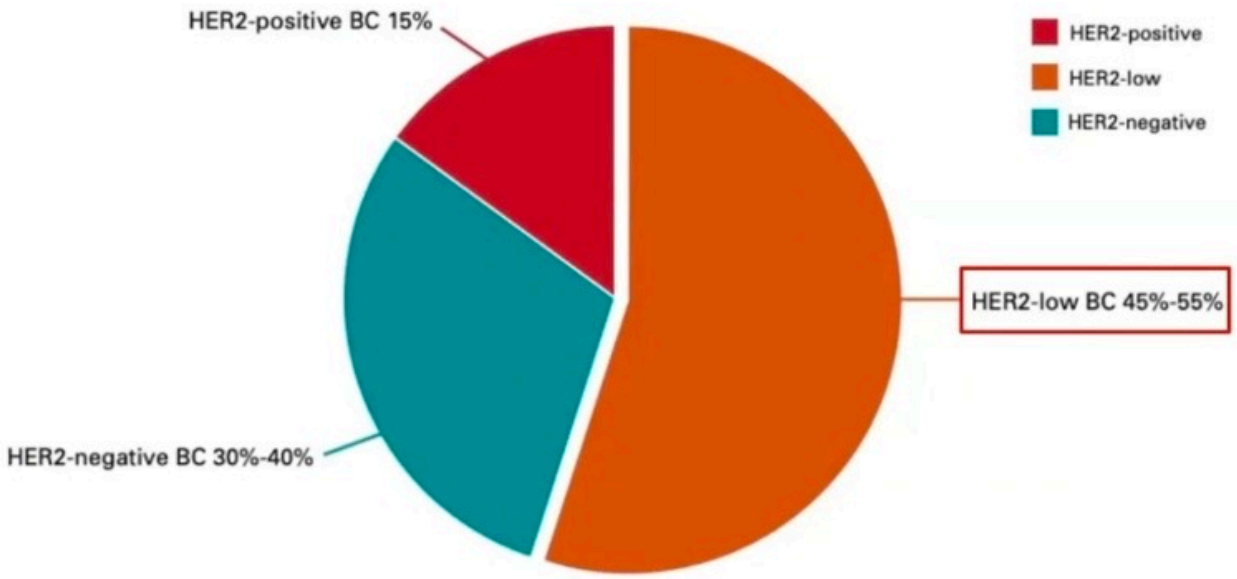


ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan.
Images adapted from Vanebs K, et al. *Front Mol Biosci*. 2022;9:834651. CC BY 4.0 license available from: https://creativecommons.org/licenses/by/4.0/.
1. Wolff AC, et al. *J Clin Oncol*. 2023;41:3867–3872. 2. Denkert C, et al. *Lancet Oncol*. 2021;22:1151–1161. 3. Chen Z, et al. *Breast Cancer Res Treat*. 2023;202:313–323. 4. Mehta S, et al. *J Clin Oncol*. 2024;42(Suppl. 16):Abstract e13156.

Curigliano G, et al. ASCO 2024. Abstract LBA1000.

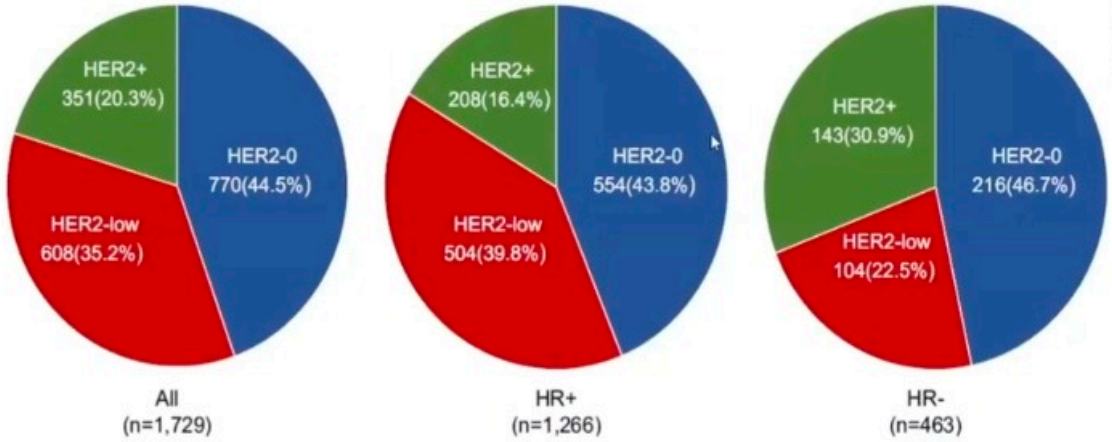
BROWN @DrSGraff

HER2-low Breast Cancer (IHC 1+ or 2+/ISH negative)



Tarantino, et al. J Clin Oncol 2020

- Low HER2 Expression in breast cancer subtypes[1]

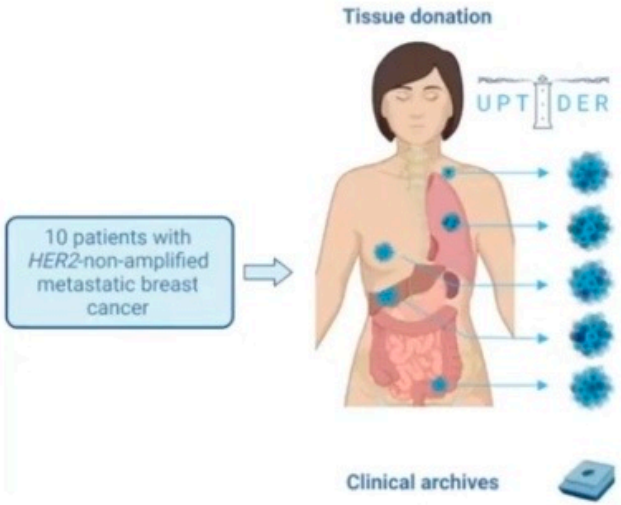


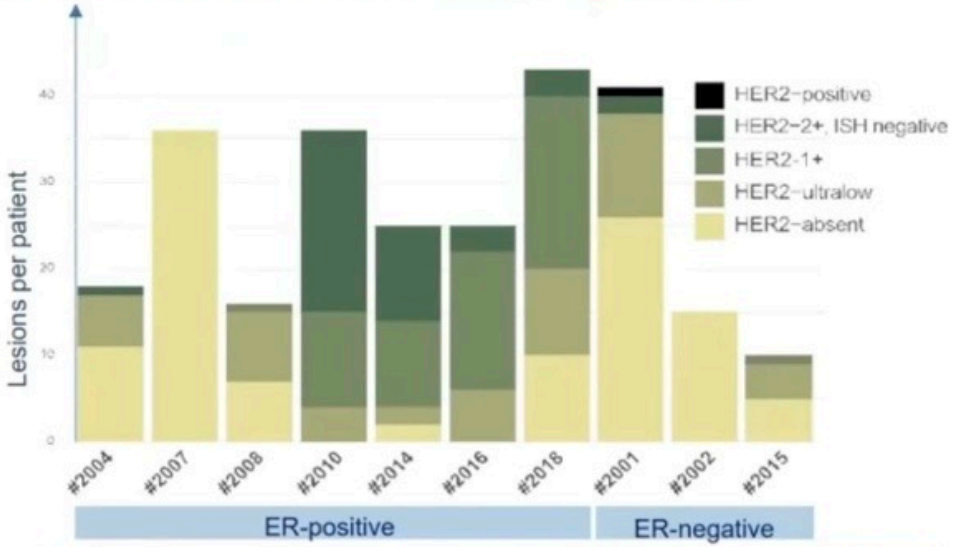
Patterns of HER status according to HR-expression, data from the AGMT mBC Registry

- Retrospective international cohorte: HER2 low in mTNBC: 30%[2]

1 Gampenrieder SP et al. Breast Cancer Res 2021;23:112.; Gampenrieder SP et al. ESMO Open 2023;8:100747.

Discordance seen within a patient with tissue from different locations at the same timepoint

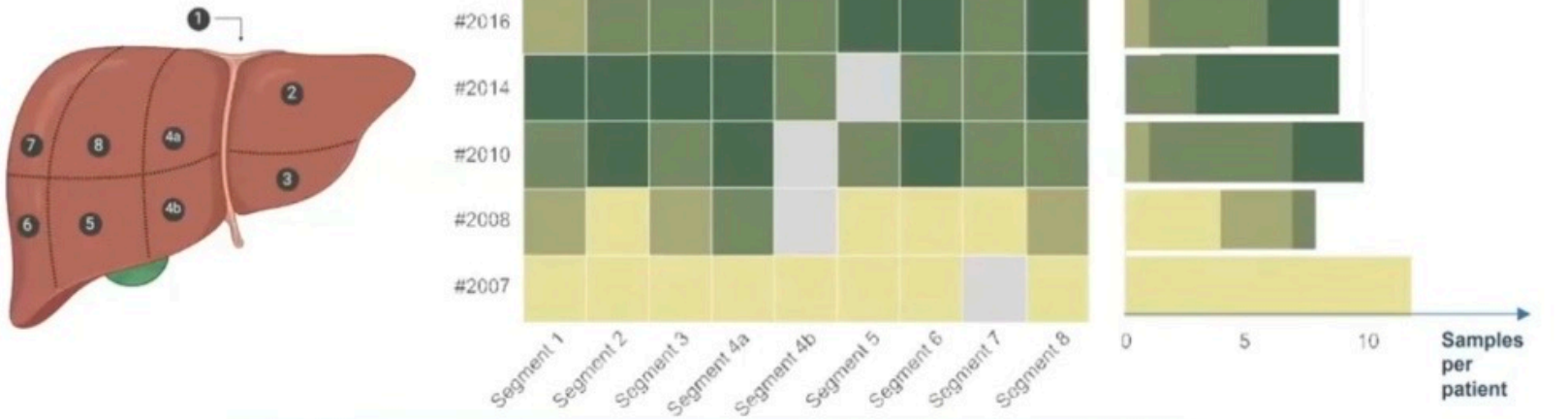




HER2-status of different metastases was highly variable within one patient, with HER2-low and zero lesions in 8/10 patients

Geukens T el al, SABCS 2022, Tolaney S, SABCS 2022

Discordance even within one organ within a patient



5 of 6 patients with heterogeneity in HER2 status from different segments of the liver

HER2-Low: Unstable Expression

		HER2 recurrence/metastasis N,%			Total
		0	Low	Positive	
HER2 primary BC N,%	0	96 (28.6)	72 (21.4)	9 (2.7)	177 (52.7)
	Low	64 (19.0)	87 (25.9)	8 (2.4)	159 (47.3)
Total		160 (47.6)	159 (47.3)	17 (5.1)	336 (100)

		HER2 recurrence/metastasis N,%			Total
		0	Low	Positive	
HER2 primary BC N,%	0	36 (45.6)	11 (13.9)	4 (5.1)	51 (64.6)
	Low	13 (16.5)	14 (17.7)	1 (1.3)	28 (35.5)
Total		49 (62.1)	25 (31.6)	5 (6.4)	79 (100)

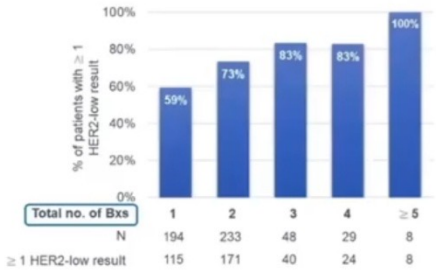
Fig. 3 HER2 expression evolution from primary BC to relapse according to breast cancer phenotype. a HR-positive/HER2-negative phenotype. **b** triple-negative phenotype. BC breast cancer, N number.

Migleatta F et al. NPJ Breast Cancer 2021

HER2 enrichment

Single institution TNBC database

- 512 patients, >1bx with HER2 status
- With each successive biopsy, 1/3 patients that were $HER2^{0}$ converted to $HER2^{low}$

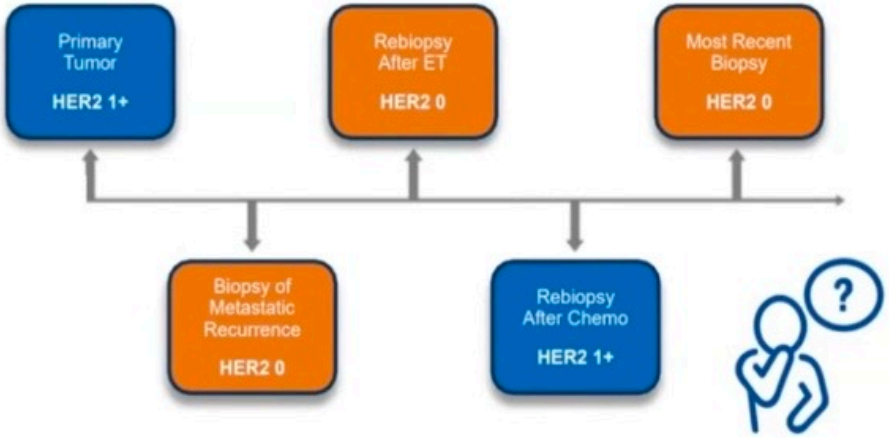


The probability of a HER2-low result increases with the total number of Bxs

Bar, ASCO, 2023

Dynamic Definition (Real Life)

- HER2-low status changes over time
- Which timepoint to use to define a tumor as HER2 low?



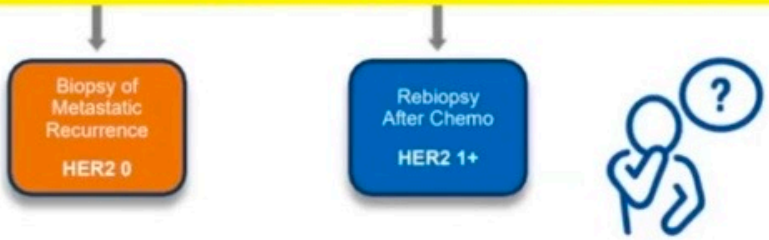
Tarantino P et al. *J Clin Oncol*. 2020;38:1951-1962.

Dynamic Definition (Real Life)

- HER2-low status changes over time
- Which timepoint to use to define a tumor as HER2 low?

Some suggestion of activity of T-Dxd irrespective of timepoint of tissue collection, definition of HER2 LOW is:

HER2 LOW expression on any prior specimen in the course of disease



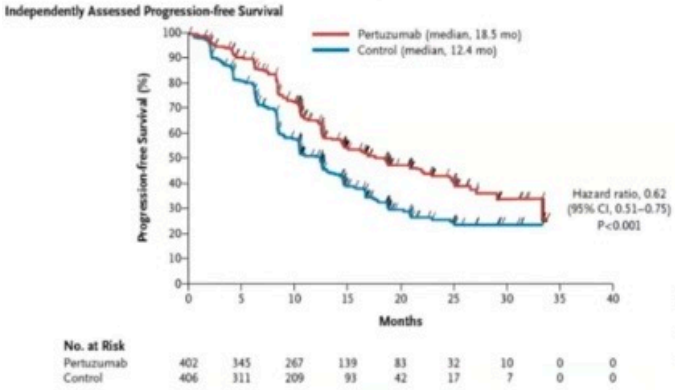
Tarantino P et al. *J Clin Oncol*. 2020;38:1951-1962.

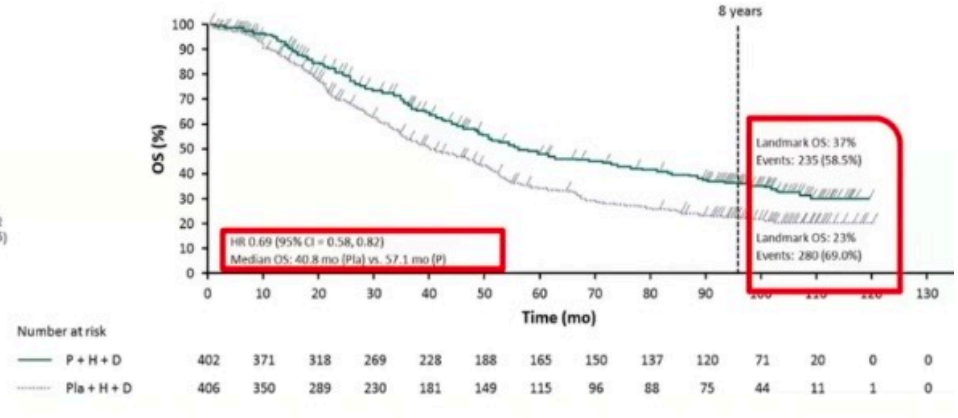
Treatment: Case 3

45-year-old woman with a history of stage IIIB, ER/PR negative, HER2+ breast cancer presents with metastatic recurrence to liver and bone three years out from curative therapy. Liver biopsy reveals histology similar to her original tumor. Her performance status is ECOG 0-1. You recommend:

A) HER2 directed monotherapy
B) Taxane + trastuzumab
C) Taxane + trastuzumab and pertuzumab

- CLEOPATRA: Phase III; 808 pts., mBC, HER2-pos., first-line, DT +/- pertuzumab
  - PFS: 18.5 *vs.* 12.4 months (HR 0.62; 95% CI 0.51-0.75; $p<0.001$)[1]
  - End-of-Study analysis: OS 57.1 *vs.* 40.8 months (HR 0.69; 95% CI 0.58-0.82; Δ 16.3 months)[2,3]
  - 8-years OS-Rate: 37% *vs.* 23%

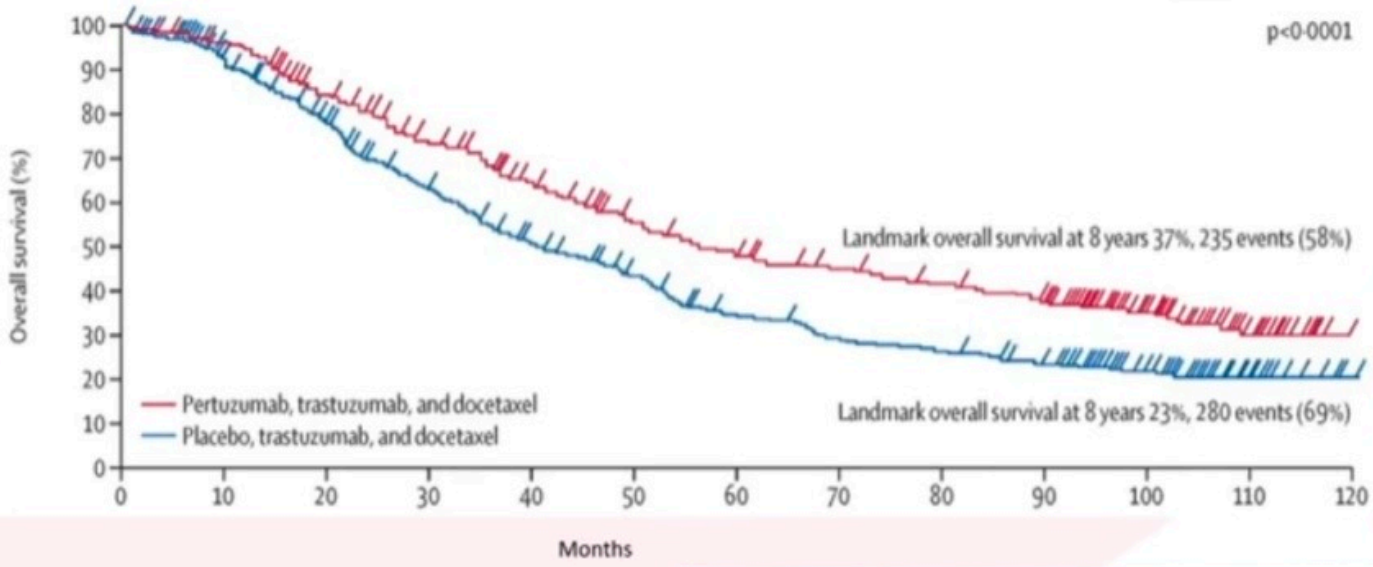




* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.
CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, pertuzumab; Pla, placebo.

1 Baselga J et al. N Engl J Med 2012;366:109-119.; 2 Swain SM et al. ASCO 2019; Abstr. #1020.; 3 Swain M et al. Lancet Oncol 2020;21:519-530.

Final Overall Survival Data from CLEOPATRA



Overall Survival: 37% in PT group vs 23% in T group

Swain SM, et al. *Lancet Oncol.* 2020 Apr;21(4):519-530.

Treatment for HER2+ MBC: Which taxane?

- PERUSE study: Patients with advanced HER2-positive breast cancer received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab + pertuzumab: Median PFS comparable among agents.
- Paclitaxel demonstrated more neuropathy (31% vs. 16%) than docetaxel, but less febrile neutropenia (1% vs. 11%) and mucositis (14% vs. 25%).
- NCCN recommends a taxane plus pertuzumab and trastuzumab in first line: Docetaxel + HP is a category 1, paclitaxel + HP is a category 2A recommendation.

Case 3, con't

Patient does well w/ THP, transitions to HP only. She receives HP injections. She does so well she lengthens her interval of scans to every 4-5 months. However, just over 2 years later, tumor markers rise, scan demonstrates e/o progression, new disease in her LNs. Next steps?

Treatment: Case 3

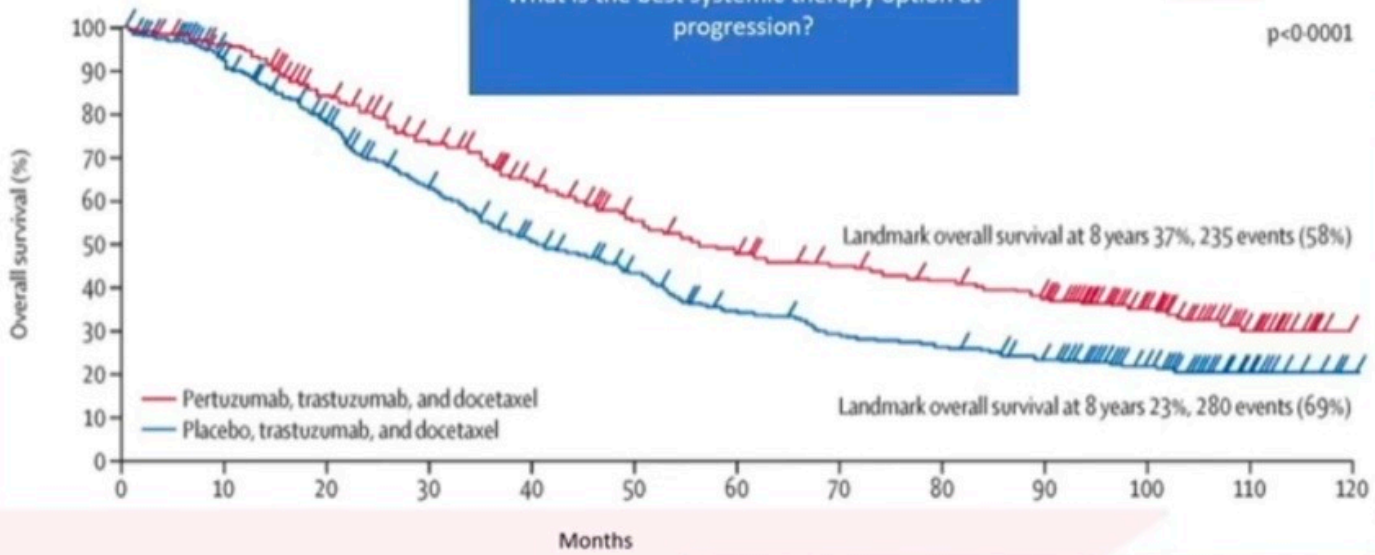
- **Answer: C, Taxane + trastuzumab and pertuzumab.**

CLEOPATRA: Compared efficacy and safety of docetaxel + trastuzuma/pertuzumab versus docetaxel + trastuzumab/placebo as first-line treatment women with HER2-positive metastatic breast cancer. The addition of pertuzumab resulted in improvement in PFS (median, 18.5 versus 12.4 months. At 30 months: Statistically significant improvement in OS for pertuzumab-containing regimen.

Baselga J, Cortes J, Kim SB, et al. N Engl J Med 2012;366:109- 119.

Final Overall Survival Data from CLEOPATRA

What is the best systemic therapy option at progression?



Overall Survival: 37% in PT group vs 23% in T group

Swain SM, et al. *Lancet Oncol*. 2020 Apr;21(4):519-530.

Case 3, con't

TDM-1: Antibody-drug conjugate, trastuzumab to the microtubule-inhibitory agent DM1 (Support for first line: MARIANNE study. Has activity and is often used in second line: EMILIA trial)

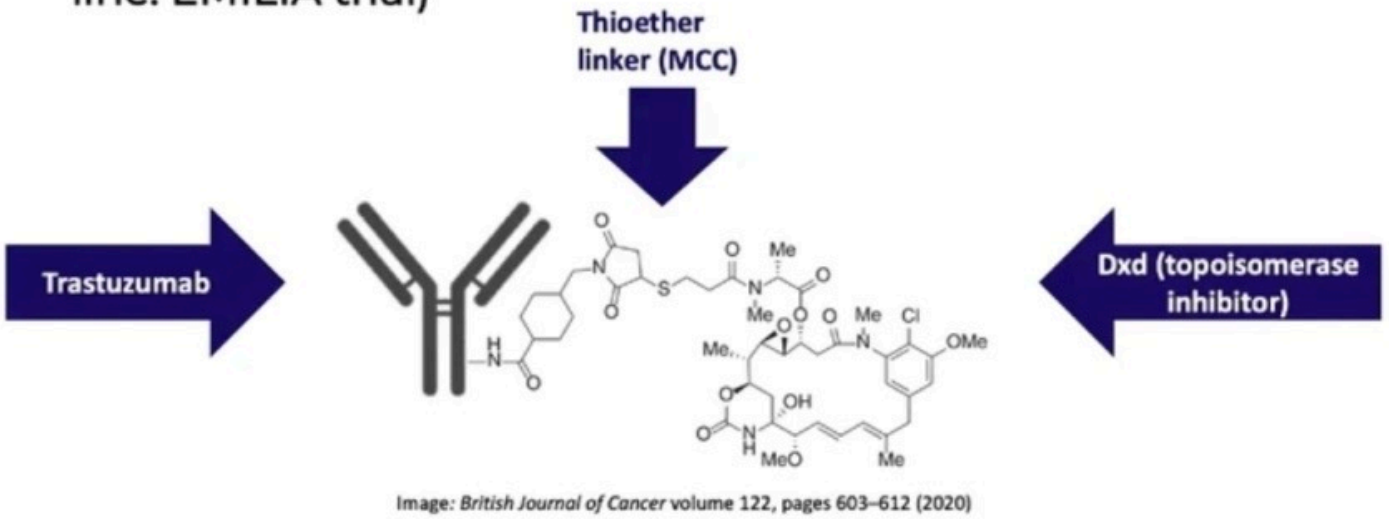
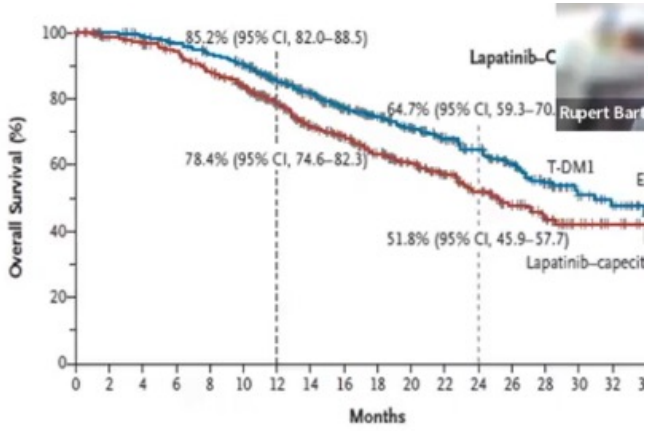


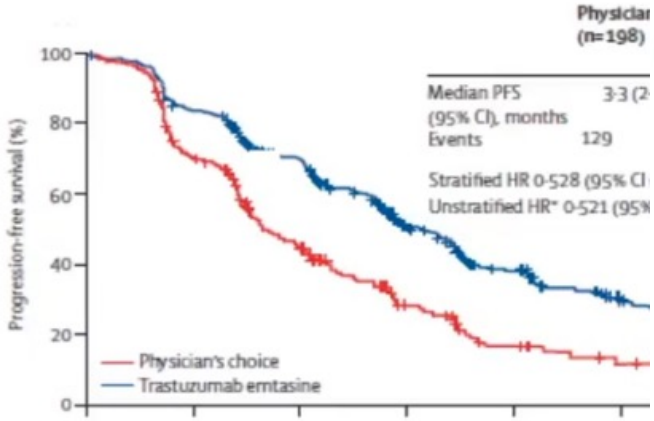
Image: *British Journal of Cancer* volume 122, pages 603–612 (2020)

T-DM1

- EMILIA: Phase III; T-DM1 *vs.* C+L[1]
  - 991 pts., mBC, predominant 2nd-line
  - PFS 9.6 *vs.* 6.4 Mo (HR 0.65; 95% CI 0.55-0.77)
  - OS 30.9 *vs.* 25.1 Mo (HR 0.68; 95% CI 0.55-0.85)



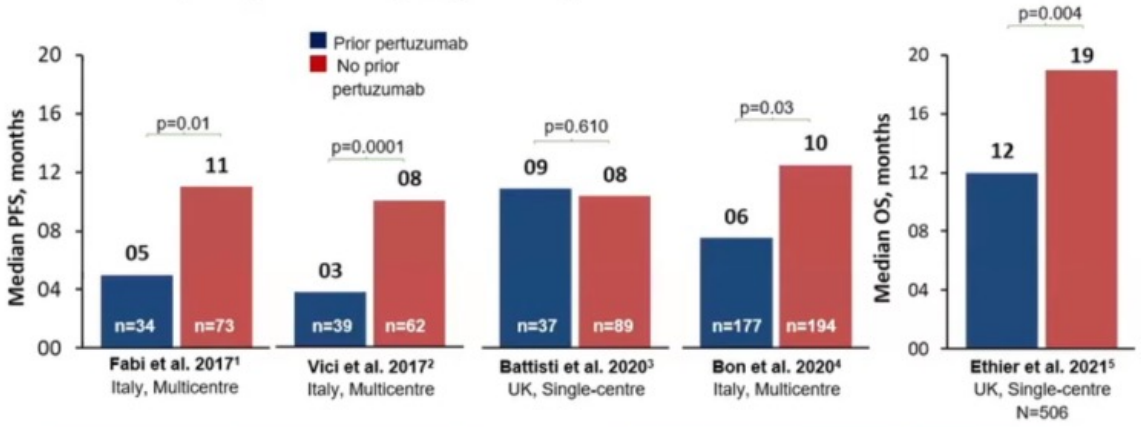
- TH3RESA: Phase III; T-DM1 *vs.* TPC (>80% trastuzumab)[2]
  - 602 pts., ≥3rd-line
  - PFS 6.2 *vs.* 3.3 Mo (HR 0.53; 95% CI 0.42-0.66)
  - OS 22.7 *vs.* 15.8 Mo (HR 0.68; 95% CI 0.54-0.85)[3]



1 Verma S et al. H Engl J Med 2012;367:1783-1791. ; 2 Krop IE et al. Lancet Oncol 2014;15:689-699.; 3 Krop IE at al. Lancet Oncol 2017;18:743-754.

T-DM1

- T-DM1: Activity in patients progressing on TP*



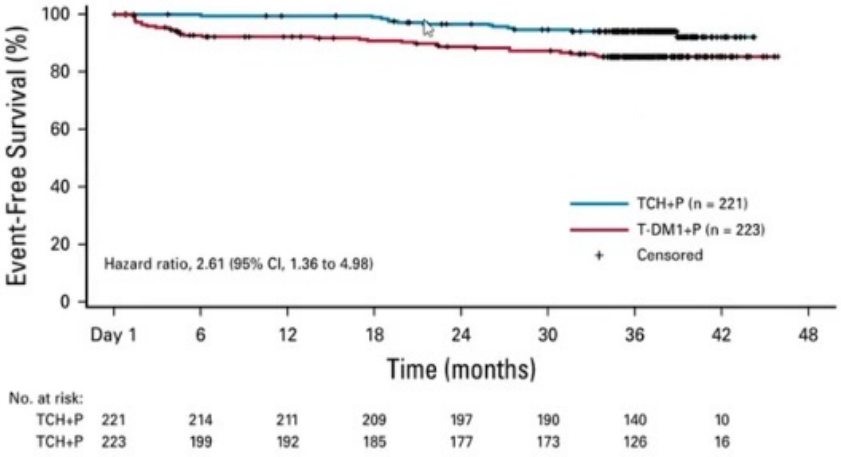
Conte et al. 2020[6]
- T-DM1 2nd line (n=77)
- Prior pertuzumab
- PFS: 6.3 months (95% CI, 4.8–7.7)

Michel et al. 2020 (PRAEGNANT registry)[7]
- T-DM1 2nd line (n=67)
- 80.3% prior pertuzumab
- PFS: 7.7 months (95% CI, 2.8–11.0)

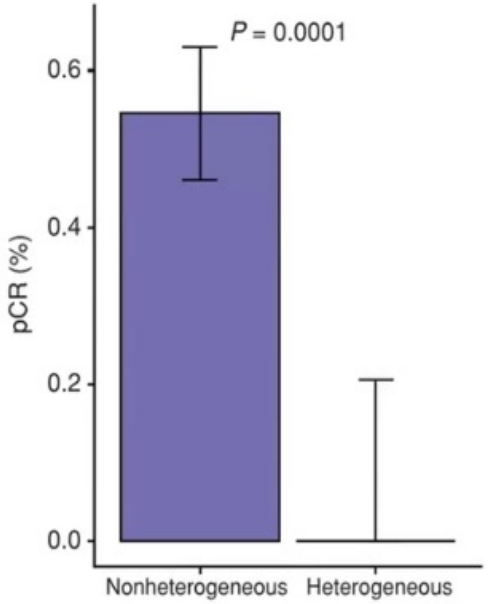
*TP, Trastuzumab + pertuzumab

1 Fabi A et al. Future Oncol 2017;13:2791-2797.; 2 Vici P et al. Oncotarget 2017;8:56921-56931.; 3 Battisti NML et al. Cancer Treat Res Commun 2020; G et al. J Exp Clin Cancer Res 2020;39:279.; 5 Ethier JL et al. JAMA Oncol. 2021;8:e212140.; 6 Conte B et al. Clin Breast Cancer 2020;20:e181–e187.; Cancers (Basel) 2020;12:3021.

- KRISTINE: T-DM1 plus pertuzumab *vs.* DCb+TP[1,2]
  - Randomized phase III trial, HER2-pos., neoadj., *n*=444 pts.
  - pCR 44.4% *vs.* 55.7% (Δ-11.3%; 95% CI -20.5 – -2.0; *p*=0.016)



- Heterogeneity 16/157 pts. (10%)
- Definition: HER2 pos. areas >5% but <5



DCb+TP: Docetaxel, Carboplatin + Trastuzumab/Pertuzumab

1 Hurvitz S et al. Lancet Oncol 2018;19:115-126.; 2 Hurvitz S et al. J Clin Oncol 2019;37:2206-2216.; 3 Metzger Filho O et al. Cancer Discov 2021t;11:2474-2487.

Newer agents for HER2+ MBC: Trastuzumab deruxtecan

- DESTINY-Breast01: Patients with HER2 positive disease previously treated with trastuzumab, untreated or symptomatic brain metastases excluded.
- Primary endpoint was overall response rate: 60.9% (95% CI, 53.4 to 68.0), of which 6.0% had a complete response. Disease control rate was 97.3% (95% CI, 93.8 to 99.1).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

ABSTRACT

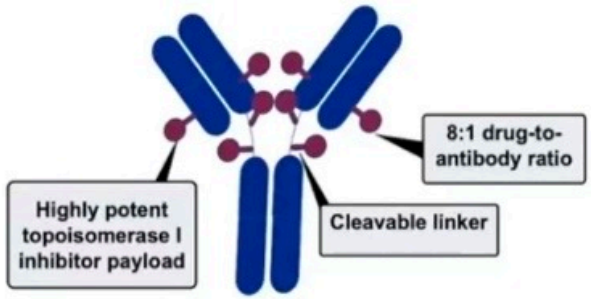
BACKGROUND

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. In a phase 1 dose-finding study, a majority of the patients with advanced HER2-positive breast cancer had a re-

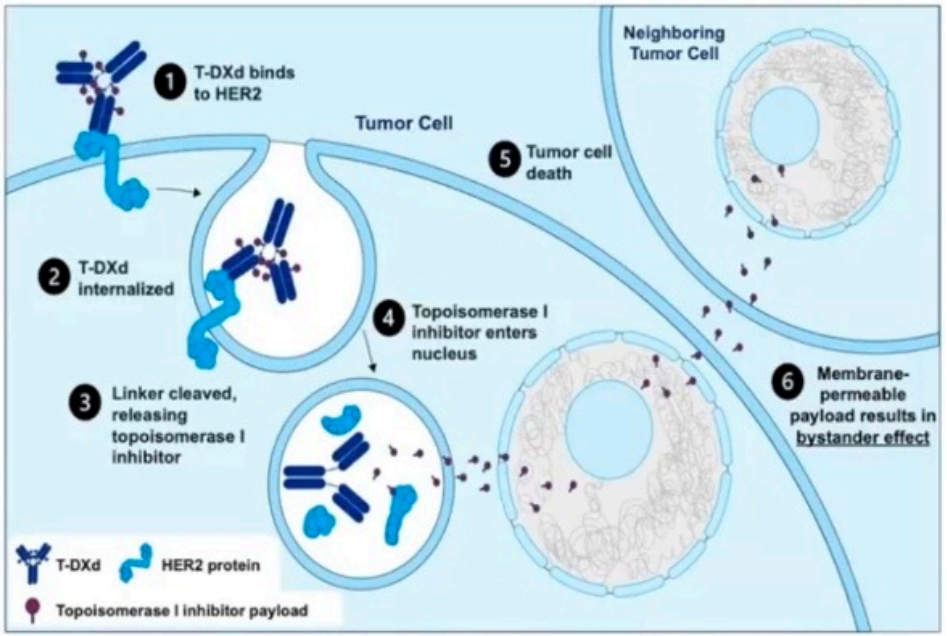
Modi S et al. N Engl J Med 2020;382:610-21.

Trastuzumab Deruxtecan (T-DXd): HER2 Antibody Drug Conjugate (ADC)

MOA, Bystander Effect, and Rationale for Targeting HER2-Low MBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect

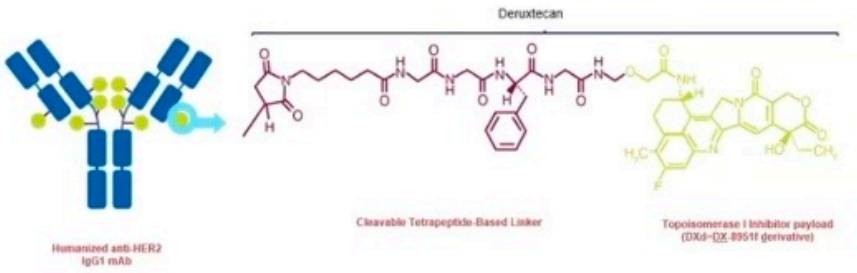


Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

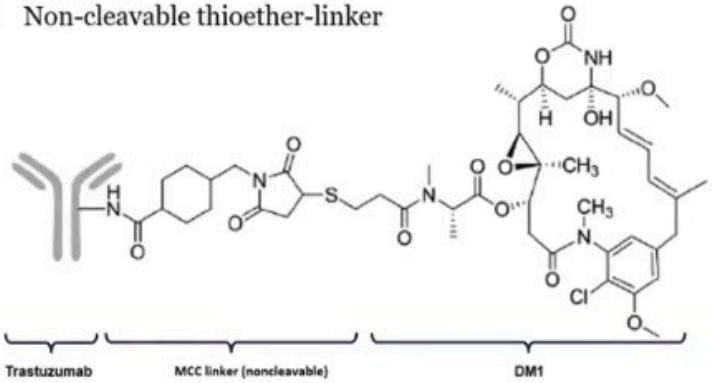
1. Nakada T, et al. *Chem Pharm Bull.* 2019;67:173-85. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Modi S, et al. *J Clin Oncol* 2020;38:1887-96.

- Trastuzumab Deruxtecan (T-DXd)[1]
  - Combination of trastuzumab and derxutecan
  - Deruxtecan (MAAA-1181a): exatecan derivative
  - Topisomerase-1 Inhibitor
  - 20x larger potency than SN38
  - Inreased membrane permability
  - Drug-to-Antibody Ratio (DAR) 8:1
  - Cleavable tetrapeptide-bases linke (stable in plasma)



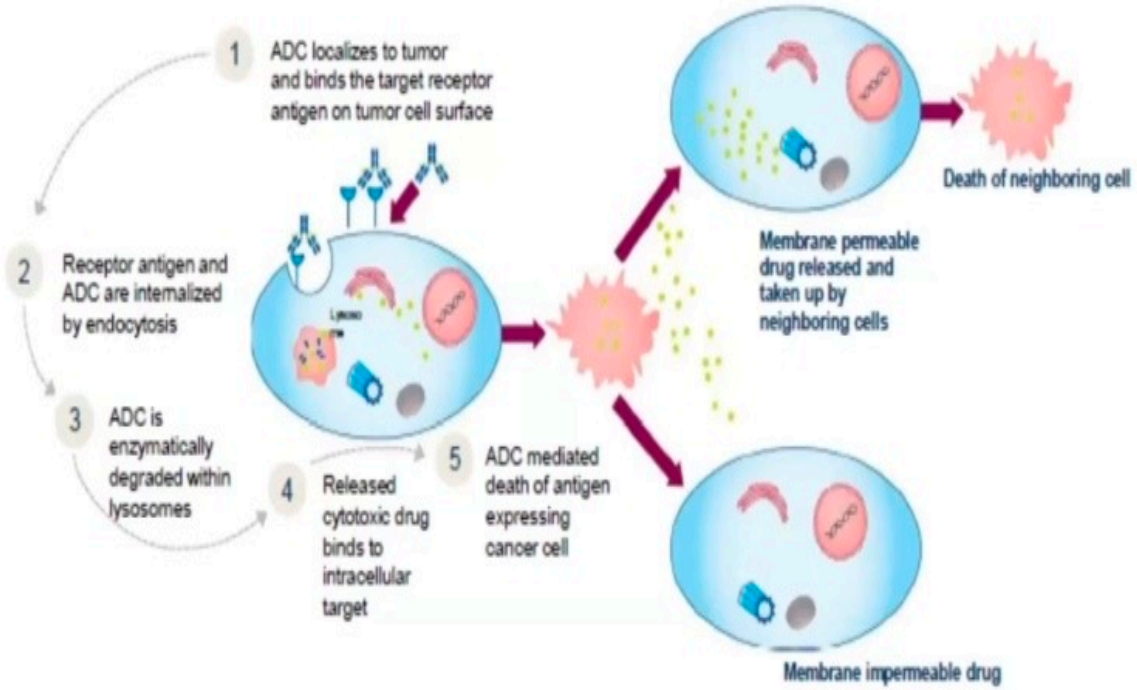
1 Reviewed in: Bartsch R. Expert Opin Investig Drugs 2020;29:901-910.

- Trastuzumab Emtansine (T-DM1)[1-3]
  - Combination of trastuzumab and Dm-1
  - DM-1: Maytansine derivative
  - Antimicrotubule agent
  - 24-270x larger potency compared with taxanes
  - DAR 3.5:1
  - Non-cleavable thioether-linker



1 Krop IE et al. J Clin Oncol 2010;28:2698-2704.; 2 Marcoux J et al. Protein Sci. 2015;24:1210-1223.; 3 Sochaj AM et al. Biotechnol Adv 2015;33:775-784.

- Bystander Effekt[1]



1 Trail PA et al. Pharmacol Ther 2018;181:126-142.

DESTINY-Breast03

Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic **HER2-positive** breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy

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)
- Safety

Stratification factors

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

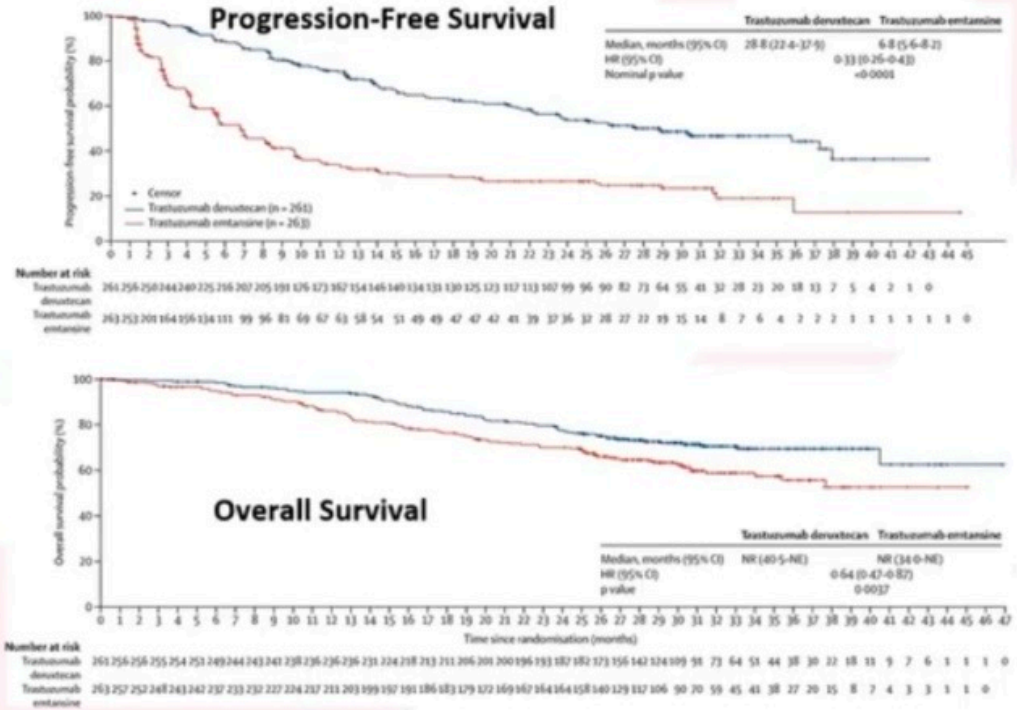
Cortes J, et al. *N Engl J Med* 2022; 386:1143-1154. Hurvitz S, et al. *Lancet*. 2023 Jan 14;401(10371):105-117.

BICR: blinded independent central review

Trastuzumab Deruxtecan (T-DXd) in Second Line HER2 + MBC

- Median follow-up 28.4 months
- Median PFS: **28.8 months** T-DXd vs **6.8 months** for T-DM1 (HR, 0.33; *P*< .0001)
- Median OS not yet reached in both arms: 72 events with T-DXd vs 97 events with T-DM1 (HR, 0.64; *P*=.0037)
- Similar grade 3 toxicities (anemia; fatigue; thrombocytopenia) in both arms
- **Drug-related interstitial lung disease/pneumonitis:*** 39 (15 %) with T-DXd vs 8 (3 %) with T-DM1

*majority grade 1 and 2; median time to onset 8.1 months (4.3 to 15 months); 70 % resolved



Hurvitz S, et al. *Lancet.* 2023 Jan 14;401(10371):105-117

T-DXt in “HER2 low” disease

- DESTINY-Breast04: T-DXt vs. physician’s choice of chemotherapy in patients with low HER2 expression.
- 52.3% overall response vs. 16.3% in the control, with 12 patients in the T-DXt group achieving a complete response.
- Improved longer progression-free survival and overall survival
- Aug 2022: FDA approves T-DXt for ”HER2 low” subtype (IHC 1+ or 2+/ISH negative)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

ABSTRACT

BACKGROUND

Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these “HER2-low” cancers.

METHODS

We conducted a phase 3 trial involving patients with HER2-low metastatic breast cancer who had received one or two previous lines of chemotherapy. (Low expression of HER2 was defined as a score of 1+ on immunohistochemical (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization.) Patients were randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan or the physician’s choice of chemotherapy. The primary end point was progression-free survival in the hormone receptor–positive cohort. The key secondary end points were progression-free survival among all patients and overall survival in the hormone receptor–positive cohort and among all patients.

The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Dr. Modi can be contacted at modis@mskcc.org or at the Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

*A list of the principal investigators in the DESTINY-Breast04 trial is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2203690

DESTINY-Breast04: First Phase 3 RCT of T-DXd in HER2-low mBC

Protocol

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

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−

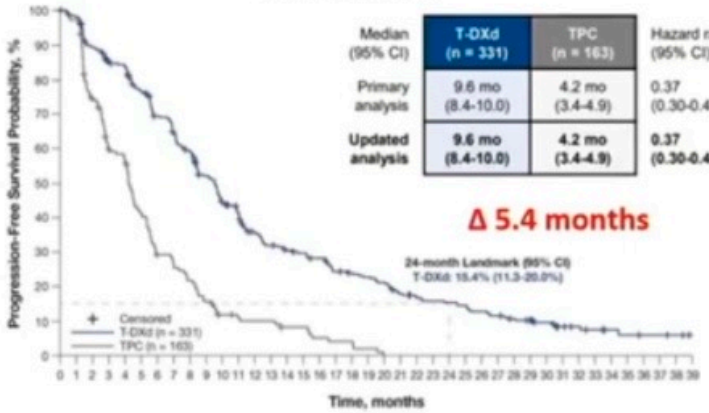
Modi S, et al. *N Engl J Med.* 2022 Jul 7;387(1):9-20.

DESTINY-Breast04: T-DXd vs Chemotherapy for Previously Treated HER2-Low MBC — PFS

HR+ Cohort

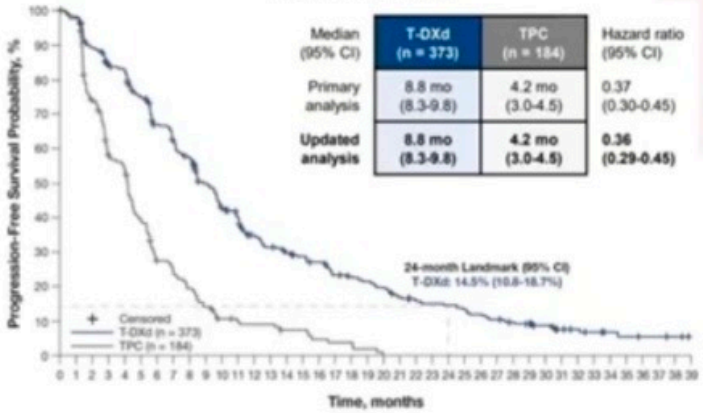
	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

Δ 5.4 months



All Patients

	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

Modi S, et al. ESMO 2023. Abstract 376O.

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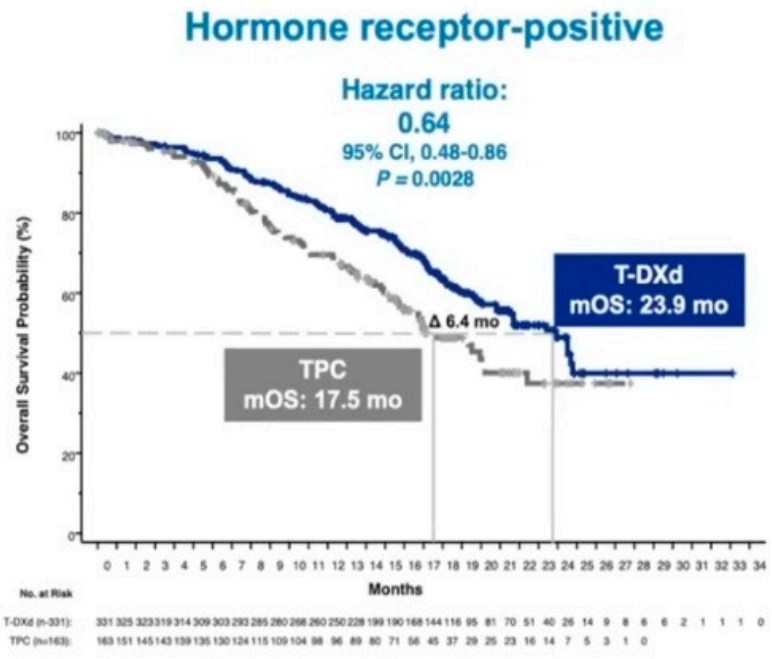
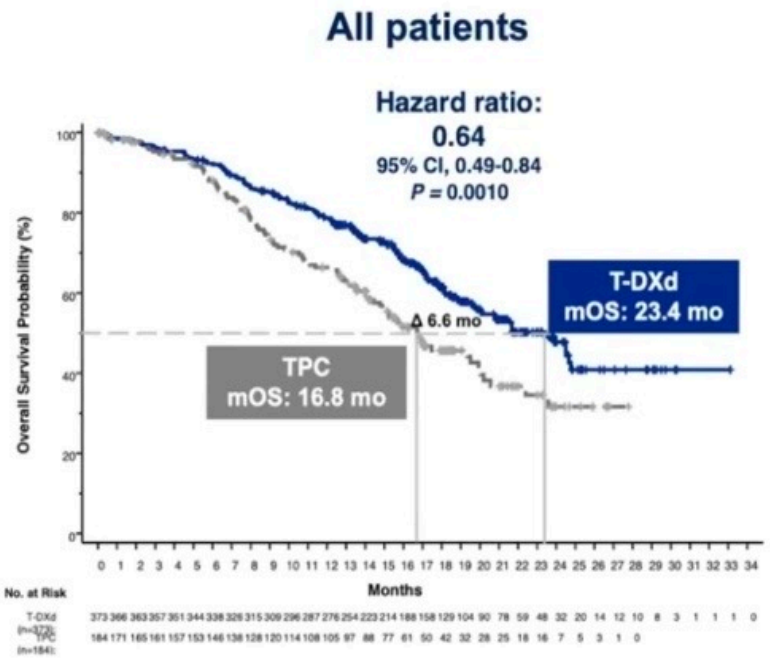
OS in HR+ and All Patients





Modi S, NEJM 2022

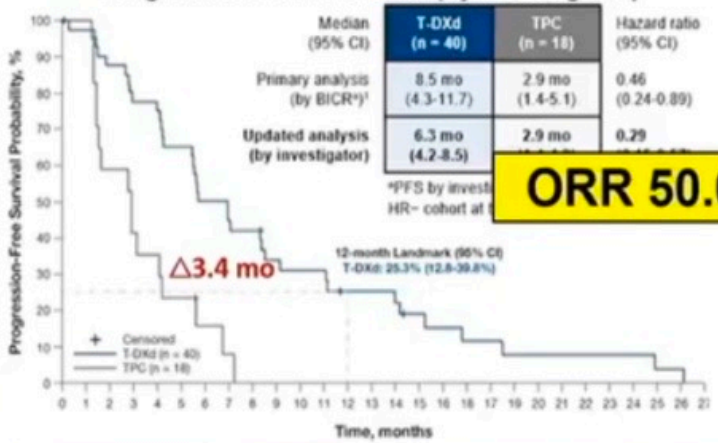
DESTINY-Breast04: PFS and OS in HR–, HER2-low mBC

(Exploratory)

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	0.29

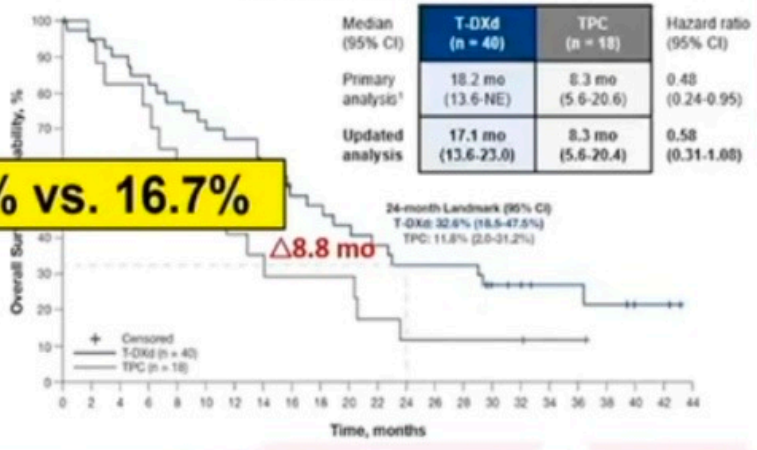
[a]PFS by invest
HR− cohort at



ORR 50.0% vs. 16.7%

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)



FDA approval of trastuzumab deruxtecan for HR-negative HER2-low mBC

Modi S, et al. ESMO 2023. Abstract 376O.

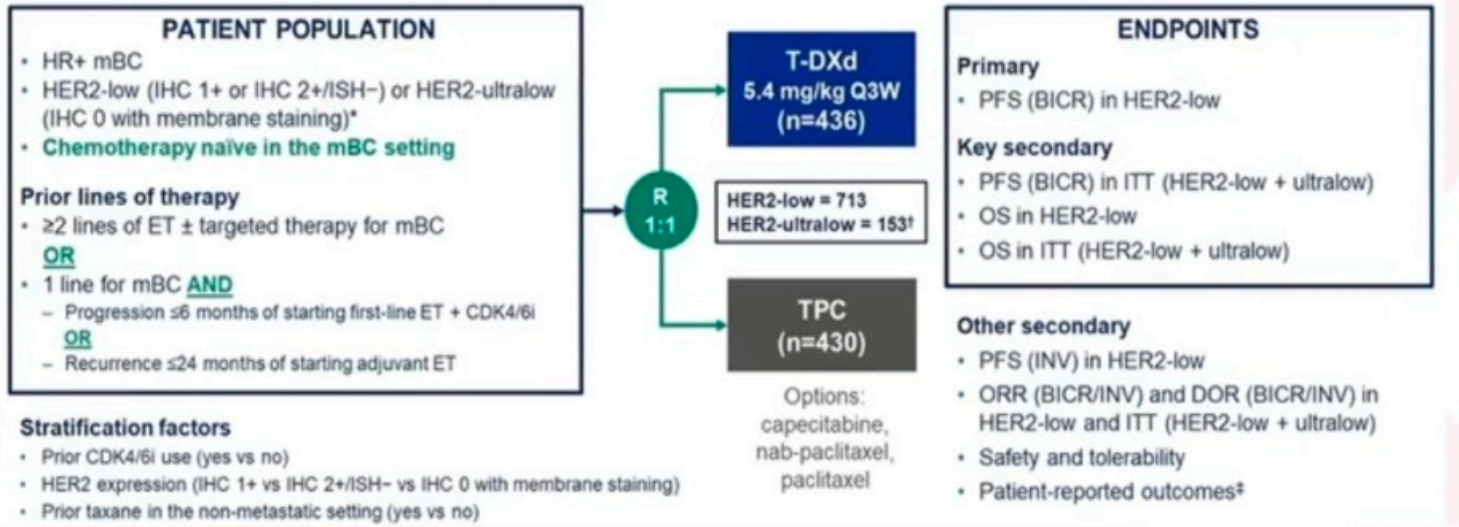
How low and early can we go with HER2 in ER+ disease?

DB-06: DESTINY Breast-06: Clinical Trial of Trastuzumab Deruxtecan (T-DXd) Compared to Investigator's Choice Chemotherapy for HER2-low, Hormone Receptor Positive Metastatic Breast Cancer

- ABC/MBC
- ER+, $HER2^{low/no}$
- No prior chemotherapy
- <6m on CDK4/6 or 2 lines of prior endocrine therapy
- Enrollment complete (866 patients)
- vs Cape/taxane (paclitaxel or nab-paclitaxel

DESTINY-Breast06: T-DXd vs. TPC in HR+ HER2-low or HER2-ultralow MBC with prior ET

New #ASCO24



Curigliano G, et al. ASCO 2024. Abstract LBA1000.

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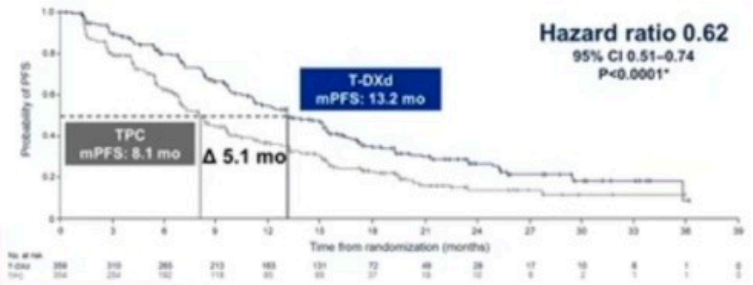
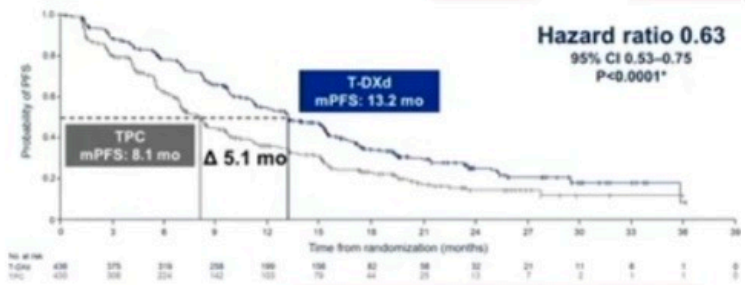
DESTINY-Breast06: PFS in HER2-low and ITT Populations

New #ASCO24

BICR PFS in HER2-low: Primary Endpoint



BICR PFS in ITT (HER2 Low & Ultralow)



Curigliano G, et al. ASCO 2024. Abstract LBA1000.

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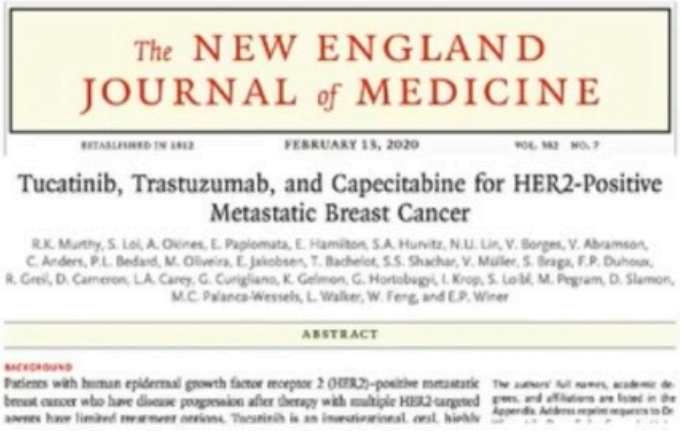
Newer agents for HER2+ MBC: Tucatinib

- HER2CLIMB: Tucatinib + trastuzumab + capecitabine
- Patients with HER2+ disease with progression on two prior lines of therapy
- PFS for Tucatinib combo vs. placebo combo 7.8 vs. 5.6 months (p<0.001)
- FDA approval in April 2020 for use after ONE prior line of therapy



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

ABSTRACT

BACKGROUND

Patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have disease progression after therapy with multiple HER2-targeted agents have limited treatment options. Tucatinib is an investigational, oral, highly

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr

Murthy et al. N Engl J Med 2020; 382:597-609

HER2CLIMB: Tucatinib, Trastuzumab and Capecitabine

- HER2-positive MBC
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status of 0 or 1
- Brain MRI at baseline
- Previously treated stable brain metastases
- Untreated brain metastases not needing immediate local therapy
- Previously treated progressing brain metastases not needing immediate local therapy
- No evidence of brain metastases

48 % of patients had BM at baseline

Randomization 2:1

Primary endpoint: PFS
Secondary: OS, RR, safety, PFS in pts with BM

Stratified by:
- Presence of brain metastases
- ECOG status (0 or 1)
- Region (US or Canada or rest of world)

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)
Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m² PO BID (Days 1-14)
N = 410

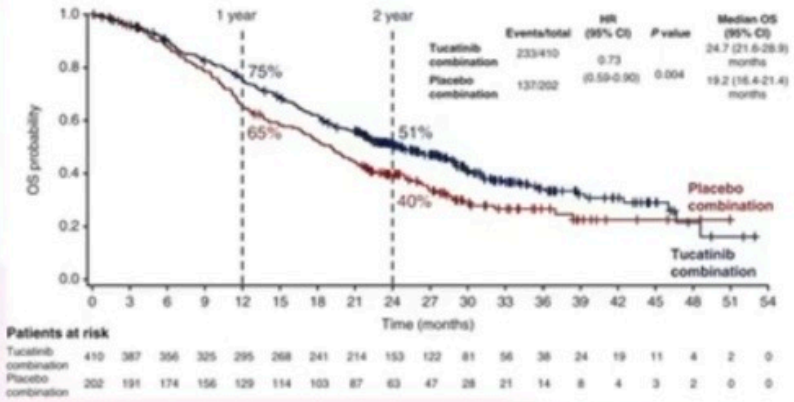
Placebo
(21-day cycle)
Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m² PO BID (Days 1-14)
N = 202

Curigliano G, et al. *Ann Oncol.* 2022 Mar;33(3):321-329. Presented at ASCO Annual Meeting 2022.

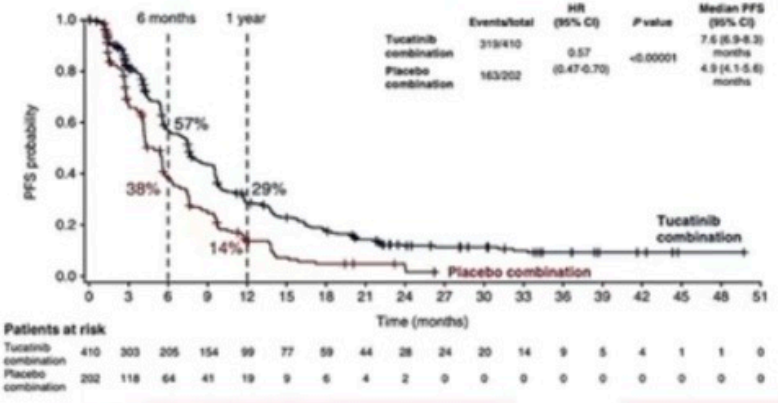
HER2CLIMB Trial: Tucatinib, Trastuzumab, Capecitabine

Median F/U of 29.6 months

Overall Survival



Progression-Free Survival



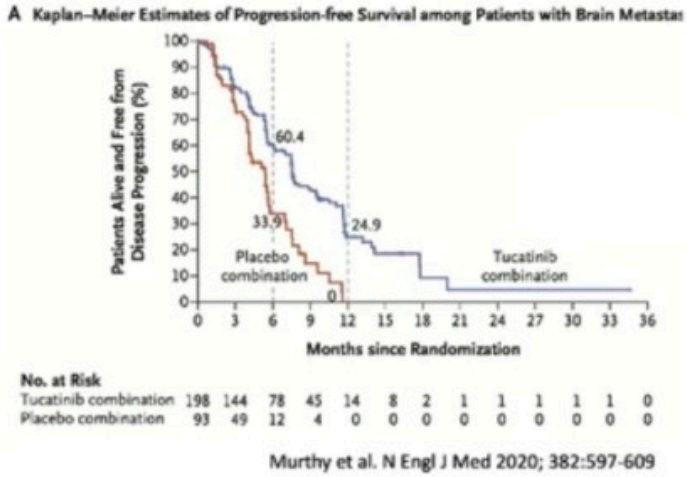
Improved OS at 2 years: 51% vs 40% (HR, 0.73, *P*=.004)

Improved PFS at 1 year: 29% vs 14% (HR, 0.54; *P* <.001)

Curigliano G, et al. *Ann Oncol.* 2022 Mar;33(3):321-329.

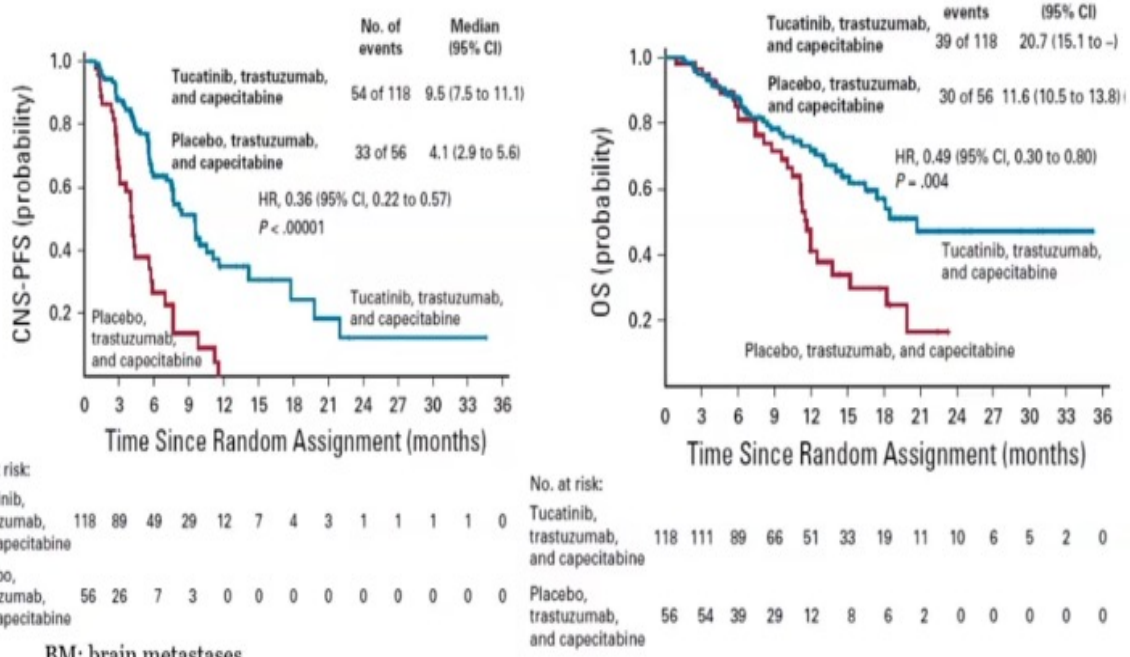
Tucatinib in patients with CNS disease

- Patients with brain metastases included unless in need of immediate treatment. Patients with untreated brain mets >2 cm enrolled with approval from the medical monitor.
- Patients with leptomeningeal disease were excluded.
- Risk of CNS progression reduced by 68% in patients with brain metastases, with a median CNS-PFS of 9.9 vs 4.2 months.



Murthy et al. N Engl J Med 2020; 382:597-609

- HER2CLIMB[1]
  - Pts. with active BM



BM; brain metastases

1 Lin NU et al. J Clin Oncol 2020;38:2610-2619.

- Patient characteristics
- 291/612 pts. in HER2CLIMB with BM at baseline (47.5%)
- 174/291 pts. active BM (59.8%)

- RR in patients with measurable BM: 47.3%

Efficacy of T-DXd and Tucatinib in HER2+ BM

Clinical Trial	Experimental Arm	Control Arm	Median PFS in BM (mo)	Median OS in BM (mo)	Median CNS-PFS (mo)		ORR-IC (%)
DB01/02/03 pooled analysis	T-DXd	Capecitabine/ Trastuzumab, Capecitabine/ Lapatinib, T-DM1	N/A	N/A	Stable BM	12.3 vs 8.7	45.2 vs 27.6
					Active BM	18.5 vs 4.0	45.5 vs 12.0
DB03	T-DXd	T-DM1	15.0 vs 3.0	NR vs 25.1	N/A		65.7 vs 34.3
HER2CLIMB	Tucatinib/ Capecitabine/ Trastuzumab	Placebo/ Capecitabine/ Trastuzumab	7.6 vs 5.4	21.6 vs 12.5	Stable BM	13.9 vs 5.6	N/A
					Active BM	9.6 vs 4.0	47.3 vs 20.0
HER2CLIMB-02	T-DM1/ Tucatinib	T-DM1/ Placebo	7.8 vs 5.7	N/A (ITT: Not significant at IA)	N/A		N/A

After T-DXd or tucatinib, activity of treatments (e.g., T-DM1, other HER2 TKIs) remains unclear

Hurvitz SA et al. ESMO 2023; Hurvitz SA et al. Lancet 2023;401:105-17; Hurvitz S et al. ESMO Open 2024;9(5):102924; Murphy R et al. N Engl J Med 2020;382:597-609; Lin NU et al. JAMA Oncol 2023;9(2):197-205; Hurvitz SA et al. SABCS 2023

Treatment for HER2+ MBC: Other regimens

- H + paclitaxel +/- carboplatin, docetaxel, vinorelbine, capecitabine
- Lapatinib + capecitabine or trastuzumab
- HER2 directed agents + anthracycline and cyclophosphamide contraindicated (27% rate of cardiac dysfunction)

Treatment for HER2+ MBC: What about HR+ disease?

- PERTAIN trial: Postmenopausal women assigned to first-line pertuzumab plus trastuzumab and an AI or trastuzumab plus an AI, with a ~3 month improvement in PFS for triplet combo
- If patient is treated initially with chemotherapy and trastuzumab plus pertuzumab, and the chemotherapy is stopped, endocrine therapy may be added.
- NCCN includes other chemo-free trastuzumab combinations (e.g., fulvestrant or tamoxifen), but should be considered only after chemotherapy plus HER2-directed therapy, or in some patients with indolent disease

Pertuzumab, Trastuzumab, and an Aromatase Inhibitor for HER2-Positive and Hormone Receptor–Positive Metastatic or Locally Advanced Breast Cancer: PERTAIN Final Analysis

Grazia Arpino[1], Juan de la Haba Rodríguez[2,3,4], Jean-Marc Ferrero[5], Sabino De Placido[1], C. Kent Osborne[6], Dirk Klingbiel[7], Valentine Revelant[8], Christine Wohlfarth[9], Raf Poppe[9], and Mothaffar F. Rimawi[6]; for the PERTAIN Study Group

ABSTRACT

Purpose: In PERTAIN's primary analysis (31 months' median follow-up), adding pertuzumab to trastuzumab and an aromatase inhibitor (AI) with/without chemotherapy significantly improved progression-free survival (PFS) in patients with previously untreated HER2-positive and hormone receptor–positive metastatic or locally advanced breast cancer (M/LABC). A potentially enhanced treatment effect was observed in patients with no induction chemotherapy. We present the final analysis (>6 years' median follow-up).

Patients and Methods: Patients ($N = 258$) were randomized 1:1 to pertuzumab (loading/maintenance: 840/420 mg) plus trastuzumab (loading/maintenance: 8/6 mg/kg) every 3 weeks and an AI (1 mg anastrozole or 2.5 mg letrozole daily; Arm A), or trastuzumab and an AI (Arm B). Induction chemotherapy was at investigator discretion. Primary endpoint: PFS. Key secondary endpoints: overall survival (OS) and safety.

Results: Median PFS was 20.6 versus 15.8 months in Arms A and B, respectively (stratified HR, 0.67; $P = 0.006$). Median OS was 60.2 versus 57.2 months (stratified HR, 1.05; $P = 0.78$). Pertuzumab treatment effect was potentially enhanced in patients with no induction chemotherapy (26.6 vs. 12.5 months). Any-grade adverse events (AE) occurred in 122 patients per arm (96.1% vs. 98.4%); grade ≥ 3 AEs in 72 (56.7%) and 51 (41.1%); serious AEs in 46 (36.2%) and 28 (22.6%).

Conclusions: The PFS benefit of pertuzumab was maintained and OS was similar between arms at final analysis. Adding pertuzumab may enhance activity in patients who do not require first-line chemotherapy for M/LABC. No new safety concerns were reported. These data provide additional evidence of the role of first-line pertuzumab and trastuzumab in HER2-positive M/LABC.

Introduction

The role of bidirectional cross-talk between HER2 and estrogen receptors in resistance to anti-HER2 and endocrine therapy has been widely studied (1–3). In the phase III CLEOPATRA study, significantly improved progression-free survival (PFS) and overall survival (OS) were observed when combining pertuzumab with trastuzumab and docetaxel compared with placebo plus trastuzumab and docetaxel for the first-line treatment of patients with HER2-positive metastatic breast cancer (4–7). On the basis of these results, pertuzumab plus trastuzumab and chemotherapy is the first-line standard of care for these patients (8). As CLEOPATRA did not permit patients to receive concomitant endocrine therapy (4, 5), the PERTAIN study (NCT01491737) was subsequently carried out to assess the value of adding pertuzumab to trastuzumab and an aromatase inhibitor (AI) with or without induction chemotherapy for the first-line treatment of patients with HER2-positive and hormone receptor–positive metastatic or locally advanced breast cancer (M/LABC) in the first randomized phase II trial of its kind (9). PERTAIN met its primary endpoint at 31 months' median follow-up, showing that the addition of pertuzumab resulted in significant improvements in PFS compared with trastuzumab and an AI alone (9). In addition, subgroups of patients who did not receive induction chemotherapy or who had a disease-free interval of ≥ 12 months since adjuvant hormone therapy experienced a potentially enhanced treatment effect (9). Here, we present updated PFS, mature OS (secondary endpoint), and updated safety results from the final analysis of PERTAIN, with a median follow-up of > 6 years.

Patients and Methods

Patients

Details of the PERTAIN study have been published previously (9). Briefly, PERTAIN was a randomized, two-arm, open-label, multicenter phase II trial conducted across 71 sites in eight countries. Eligible patients were postmenopausal (fulfilling ≥ 1 National Comprehensive Cancer Network criterion; ref. 8) with previously untreated HER2-positive and

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Members of the PERTAIN Study Group are listed in the Supplementary Data files.

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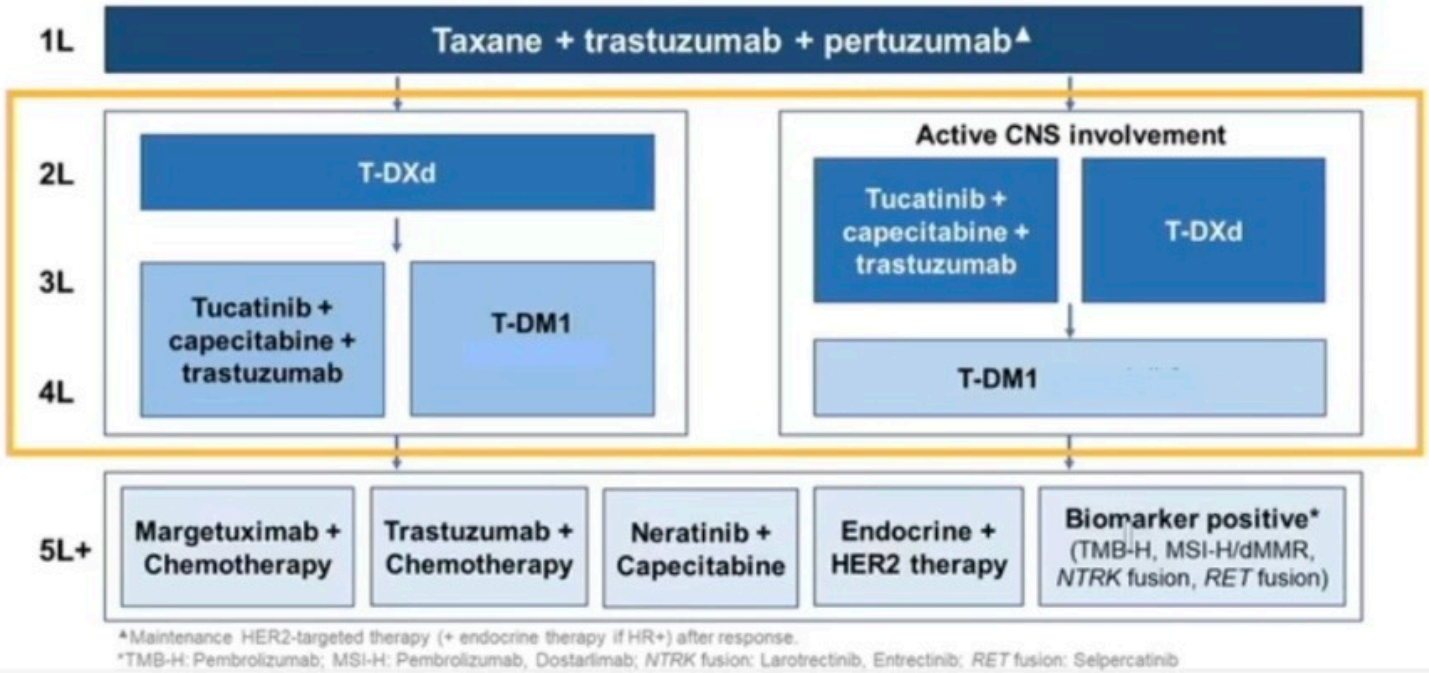
Clin Cancer Res 2023;29:1468–76

doi: 10.1158/1078-0432.CCR-22-1092

Treatment Algorithm for HER2+ MBC



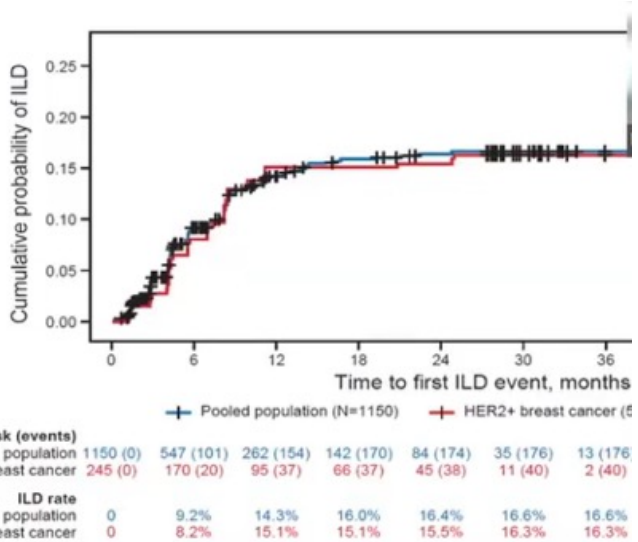
▲Maintenance HER2-targeted therapy (+ endocrine therapy if HR+) after response.
*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; *NTRK* fusion: Larotrectinib, Entrectinib; *RET* fusion: Selpercatinib

Recap for HER2+ Metastatic Disease

- ☑ **First-line** treatment includes a **taxane in combination with trastuzumab and pertuzumab**
- ☑ **Trastuzumab deruxtecan** is the current preferred agent for **second-line** treatment
- ☑ Consider tucatinib containing regimens **(HER2CLIMB/HER2CLIMB-02) for patients with active or progressing brain metastases in second-line treatment**
- ☑ **HER2CLIMB regimen recommended for third-line and T-DM1 for fourth line treatment**
- ☑ Optimal sequencing **beyond 4th line is unclear**

ILD

- ILD risk over time: Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies[1]
- Risk factors: ILD, smoking[2]



n (%)	All patients (N = 1150)	HER2+ Breast cancer 5.4 mg/kg (n = 245)[b]	Gastric cancer (n = 294)	Lung cancer (n = 203)[c]	Colorectal cancer (n = 107)	Other cancer (n = 34)
Grade 1	48 (4.2)	9 (3.7)	5 (1.7)	7 (3.4)	0	4 (11.8)
Grade 2	89 (7.7)	22 (9.0)	15 (5.1)	16 (7.9)	5 (4.7)	2 (5.9)
Grade 3	14 (1.2)	2 (0.8)	3 (1.0)	2 (1.0)	1 (0.9)	1 (2.9)
Grade 4	1 (0.1)	0	1 (0.3)	0	0	0
Grade 5	25 (2.2)	7 (2.9)	1 (0.3)	6 (3.0)	3 (2.8)	0
Total	**177 (15.4)**	**40 (16.3)**	**25 (8.5)**	**31 (15.3)**	**9 (8.4)**	**7 (20.6)**

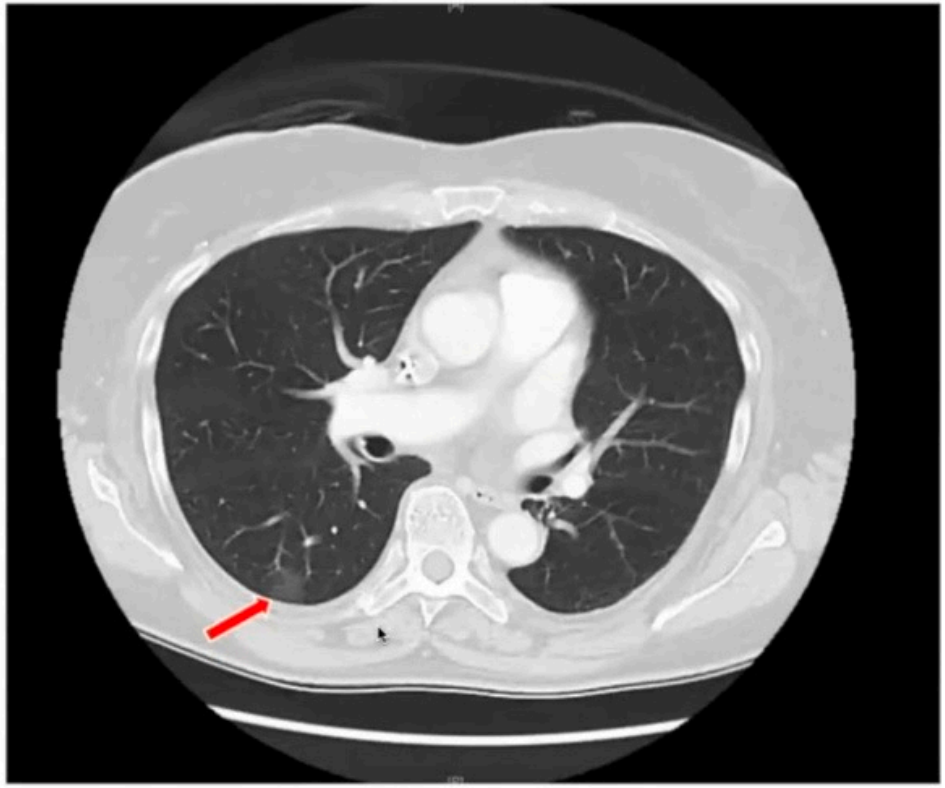
Months (range)	Pooled Analysis
Median treatment duration	5.8 (0.7-56.3)
Median time to adjudicated ILD/pneumonitis onset	5.4 (< 0.1-46.8)

1 Powell CA et al. ESMO Open. 2022;7:100554.; 2 Canellas A et al.

Grading of ILD

Grade	
1	Asymptomatic, radiographic findings only
2	Symptomatic, not interfering with activities of daily living
3	Symptomatic, interfering with activities of daily living or oxygen indicated
4	Life-threatening or ventilator support required
5	Fatal

Skeoch S, et al. *J Clin Med*. 2018;7(10):356.



Strategies to Manage ILD Associated With *HER2*-Directed ADCs

Monitor

Suspected ILD

Urge patients to immediately report cough, dyspnea, fever, and/or new or worsening pulmonary symptoms

- Monitor patients for signs/symptoms of ILD
- Promptly investigate evidence of ILD
- Evaluate patients with suspected ILD by radiographic imaging and assess as follows

Confirm

Assessments should include

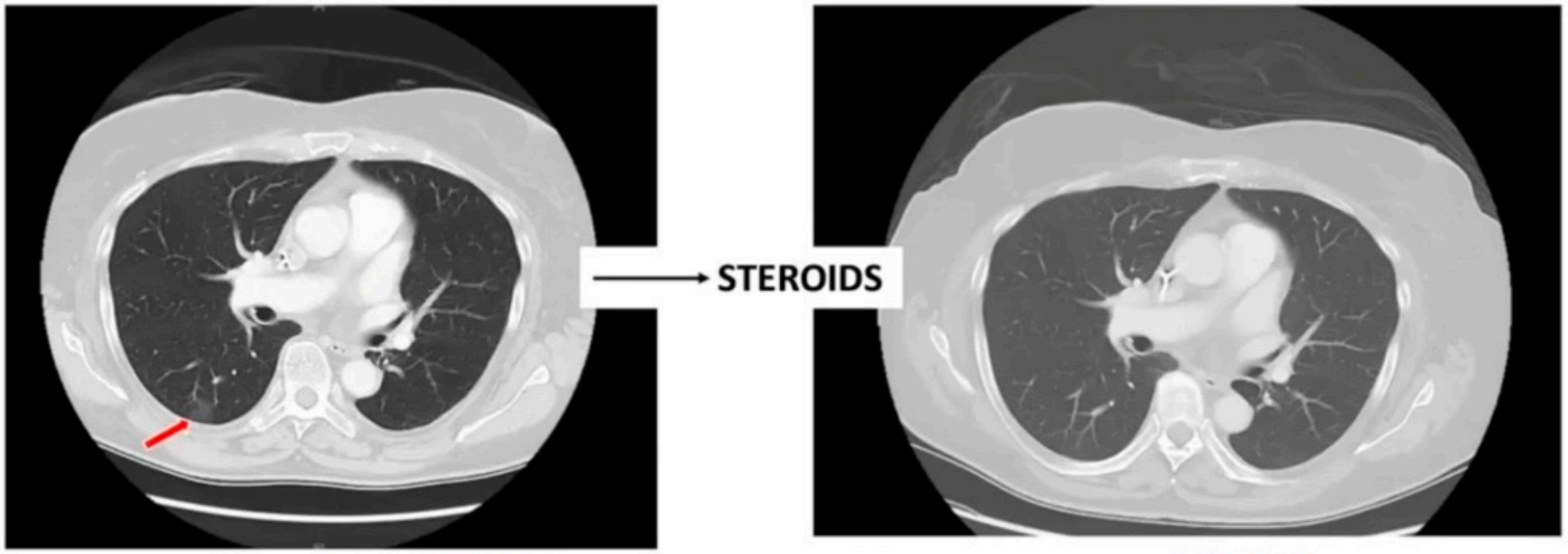
- High-resolution CT
- Pulmonologist consult
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and bronchoalveolar lavage (BAL) if indicated and feasible
- Pulmonary function tests (PFTs) and pulse oximetry
- Arterial blood gases, if indicated
- As soon as ILD suspected, collect 1 blood sample for pharmacokinetics (PK) assessment, if feasible
- Rule out other causes of ILD (eg, progression, infection, other drugs, radiotherapy)
- All ILD events should be followed until resolution and after drug discontinuation

Manage

- **Grade 1 T-DXd:** Hold until resolved to Grade 0; consider corticosteroids (0.5 mg/kg/day prednisolone), then
  - *If resolved ≤28 days from onset:* Maintain dose
  - *If resolved >28 days after onset:* Reduce dose by 1 level
- **Grades 2-4:** Permanently discontinue treatment and promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent for ≥14 days followed by taper for ≥4 weeks)

Ado-trastuzumab emtansine PI 2022 (https://www.gene.com/download/pdf/kadcyla_prescribing.pdf). Fam-trastuzumab deruxtecan-nxki PI 2022 (https://daiichisankyo.us/ prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true). URLs accessed 9.2.2022. Tarantino P, et al. *JAMA Oncol*. 2021;7(12):1873-1881.

Every 6-9 weeks CT scans



Baseline: 8/2022

9/2022

T-Dxd related nausea

	BEFORE T-DXd	Days 2-4	Days 5-21	Dose delays/ modifications
First cycle	5-HT3 receptor antagonist (RA) **(palonosetron)** + DEX	DEX ± 5-HT3 RA **OR** metoclopramide	**Olanzapine** or metoclopramide ± DEX	
Subsequent cycles, *if treatment in Cycle 1 not adequate*	NK1 receptor antagonist **(aprepitant)** ± 5-HT3 RA + DEX ± olanzapine	NK1 RA + 5-HT3 RA ± DEX **OR** DEX ± metoclopramide ± olanzapine	Same as above	Grade 3: delay dose until resolved to grade ≤1 If >7 days until resolution, reduce dose by 1 level

Rugo, Bianchini et al, 2022., slide courtesy of Julie LaBarbera, NP

Treatment: Case 4

A 58-year-old woman presents with a 6 cm clinically node positive breast tumor. Biopsy demonstrates a high-grade invasive ductal carcinoma, ER/PR/HER2 negative. Staging scans demonstrate liver involvement, which biopsy shows to be metastatic disease. PDL-1 testing with the 22C3 assay reveals a score of 15%. What therapy will you select in the first line for her?

A) Atezolizumab
B) Sacituzumab
C) Pembrolizumab
D) Avelumab

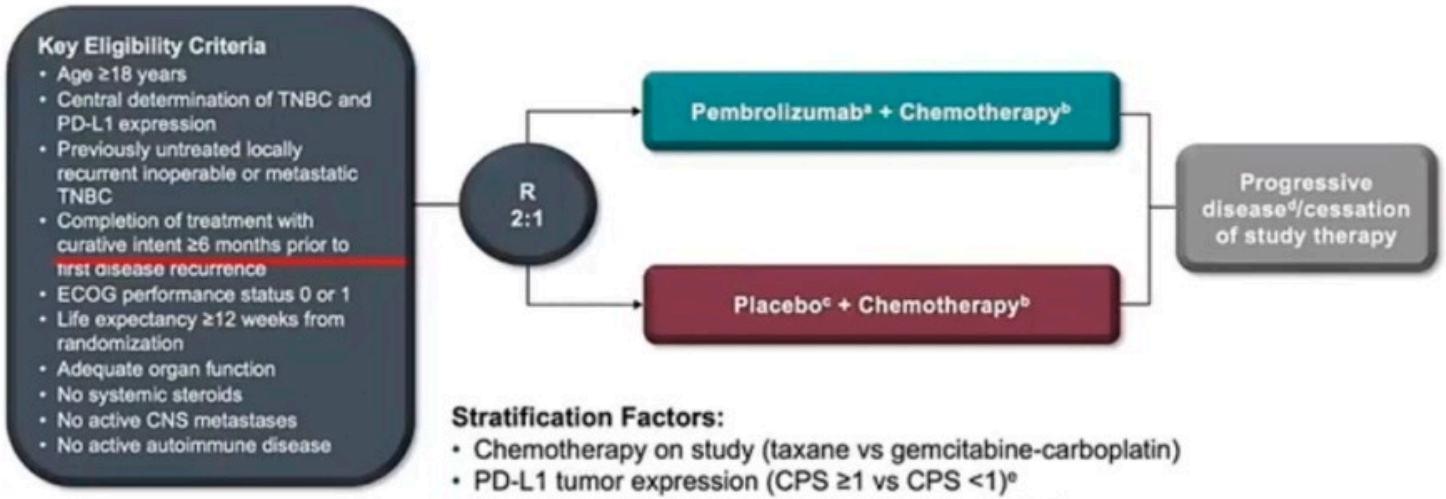
Treatment: Case 4

Answer: C, Pembrolizumab.

PDL-1 testing demonstrating combined positive score of ≥10 using the 22C3 assay supports treatment with the immune checkpoint inhibitor pembrolizumab. Guidelines recommend this therapy in the first line in eligible patients, but it can be given in subsequent lines as well.

KEYNOTE-355

Protocol



Stratification Factors:

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

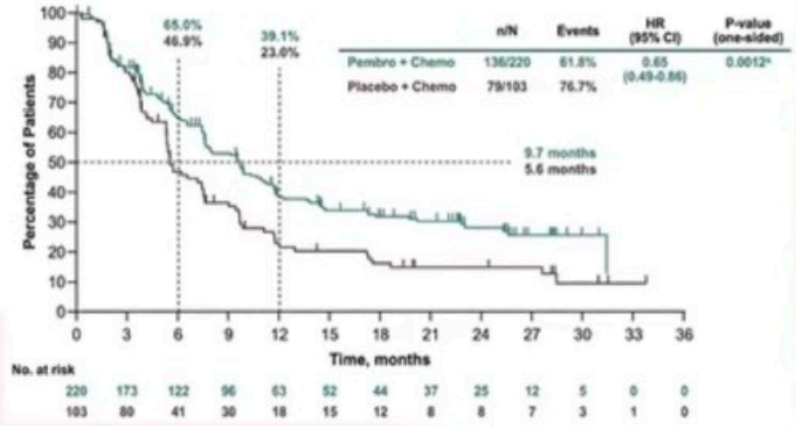
[a]Pembrolizumab 200 mg IV Q3W.
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days.
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days.
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days.

[c]Normal saline.
[d]Treatment may be continued until confirmation of progressive disease.
[e]PD-L1 CPS at cutoff 10 was not a stratification factor.

Rugo HS, SABCS 2021.

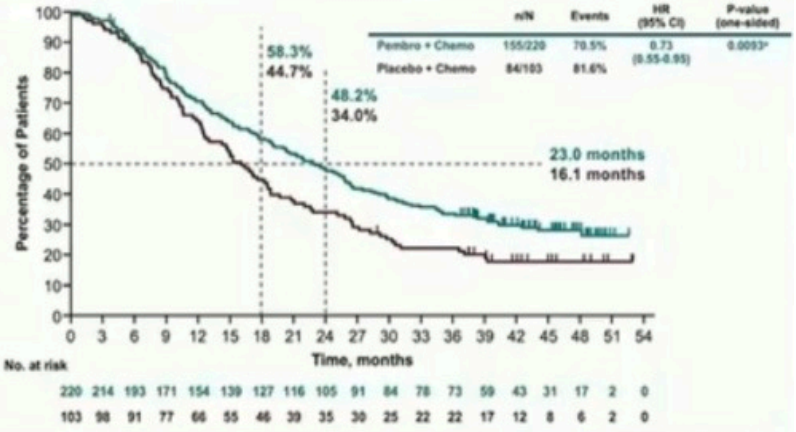
Pembrolizumab for mTNBC with PD-L1 CPS ≥ 10

Progression-free Survival



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

Overall Survival



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		

Cortes J, et al. *N Engl J Med*. 2022 Jul 21;387(3):217-226. .

Rise and fall of atezolizumab

- IMpassion 130: Atezolizumab plus nab-paclitaxel vs. placebo plus nab-paclitaxel in patients with treatment-naïve TNBC. PFS advantage and a trend toward better OS.
- March 2019: FDA granted accelerated approval for atezolizumab + nab-paclitaxel in the first line for patients with PD-L1 expressing tumors.
- Aug. 2021: TNBC indication withdrawn after IMPASSION 131 results demonstrated no PFS or OS advantage

National Comprehensive Cancer Network®

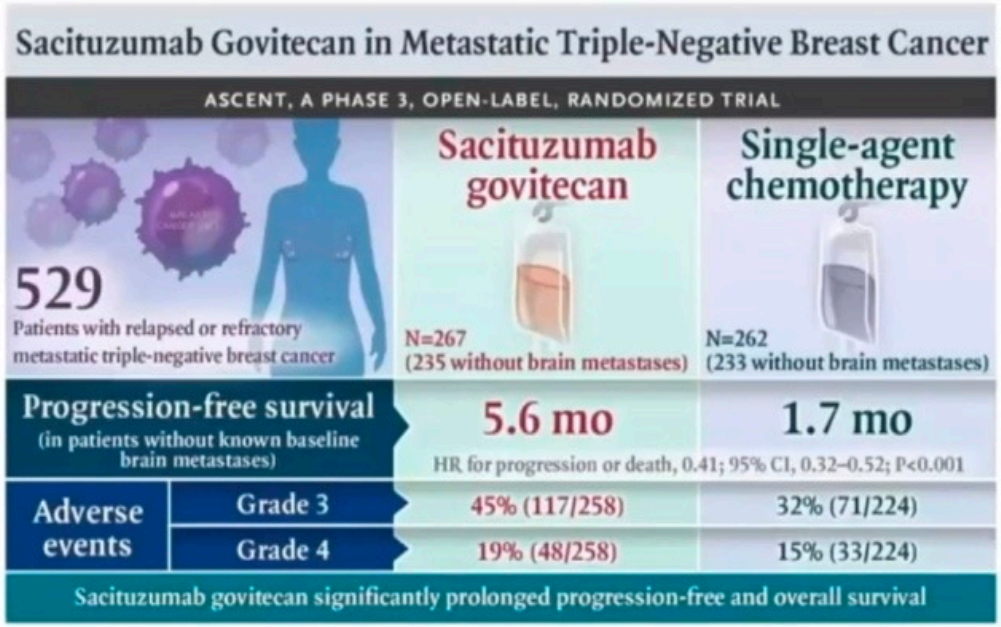
NCCN Guidelines Version 5.2023
Invasive Breast Cancer

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

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*



Chemo options:

- Gemcitabine
- Capecitabine
- Eribulin
- Vinorelbine

Sacituzumab govitecan

- Sacituzumab: ADC linking an anti-Trop-2 antibody to a topoisomerase I inhibitor
- Median overall survival was 12.1 months vs 6.7 with chemotherapy
- Objective response 35% with sacituzumab govitecan vs 5% with chemo.
- FDA approval in April 2021 for patients with MBC who have received ≥2 lines of chemo.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*

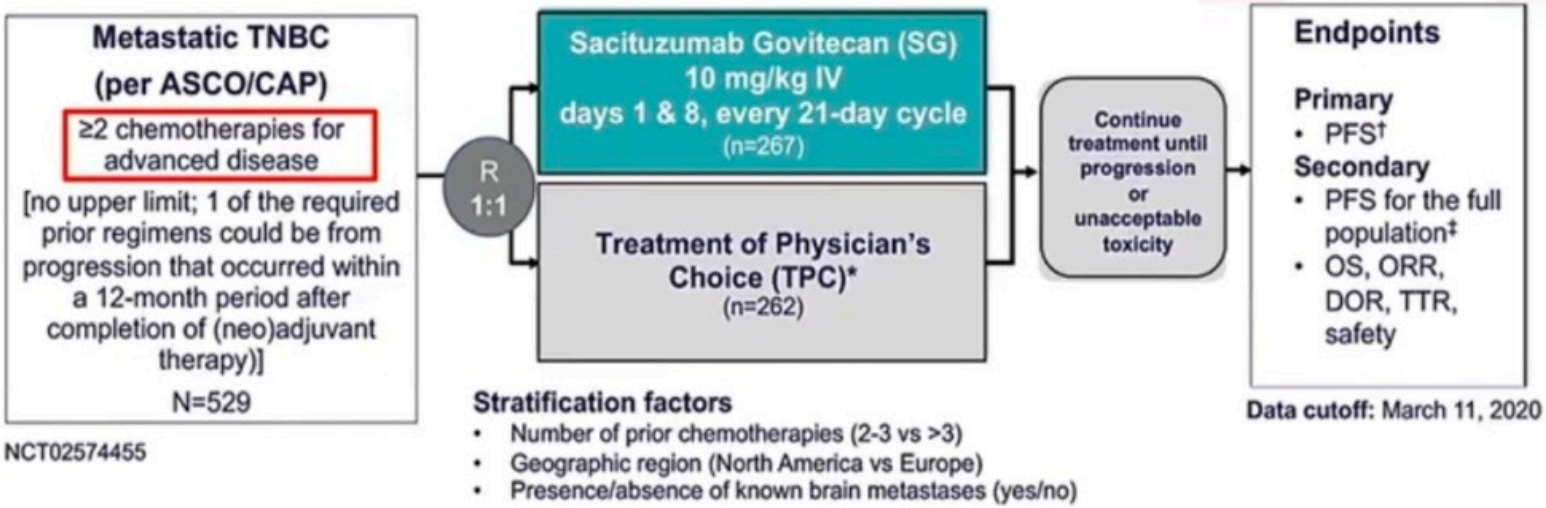
ABSTRACT

BACKGROUND

Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody–drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker.

Phase 3 ASCENT Trial: Sacituzumab Govitecan vs TPC in mTNBC

Protocol

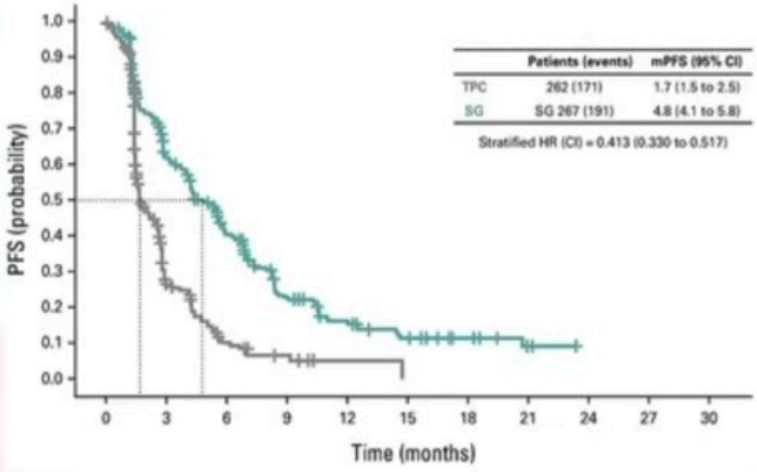


* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

Bardia A, et al. *N Engl J Med.* 2021 Apr 22;384(16):1529-1541.

Phase 3 ASCENT: Survival Endpoints, ITT Population

Progression-free Survival

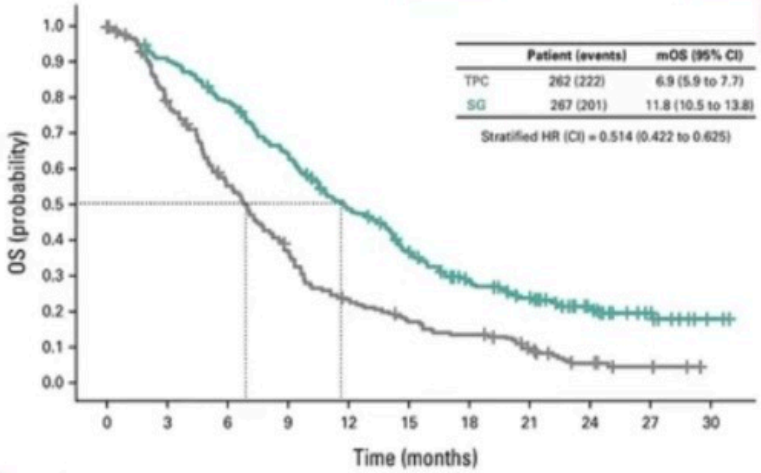


	Patients (events)	mPFS (95% CI)
TPC	262 (171)	1.7 (1.5 to 2.5)
SG	SG 267 (191)	4.8 (4.1 to 5.8)

Stratified HR (CI) = 0.413 (0.330 to 0.517)

No. at risk:									
TPC	262	40	12	5	1	0	0	0	0
SG	267	145	82	38	23	14	8	3	0

Overall Survival



	Patient (events)	mOS (95% CI)
TPC	262 (222)	6.9 (5.9 to 7.7)
SG	267 (201)	11.8 (10.5 to 13.8)

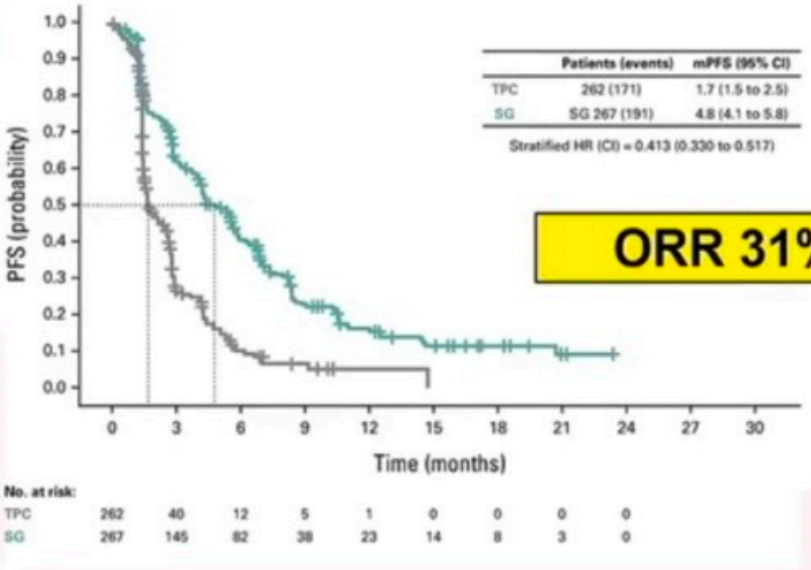
Stratified HR (CI) = 0.514 (0.422 to 0.625)

No. at risk:											
TPC	262	192	132	87	54	39	31	16	7	3	0
SG	267	242	209	169	125	92	62	42	25	11	2

Bardia A, et al. *J Clin Oncol*. 2024 May 20;42(15):1738-1744.

Phase 3 ASCENT: Survival Endpoints, ITT Population

Progression-free Survival



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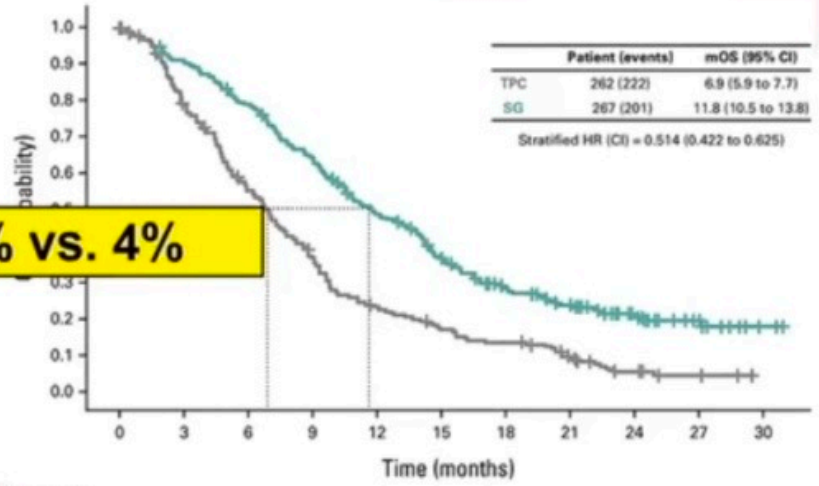
TPC	262	40	12	5	1	0	0	0	0
SG	267	145	82	38	23	14	8	3	0

ORR 31% vs. 4%

Overall Survival



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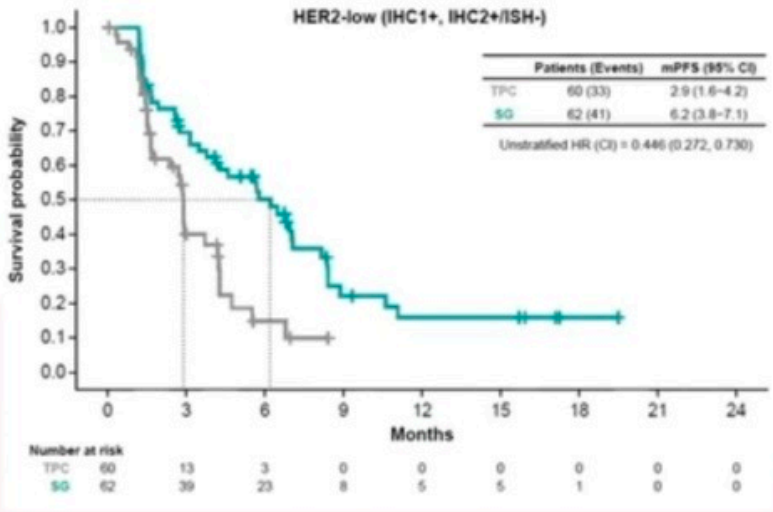
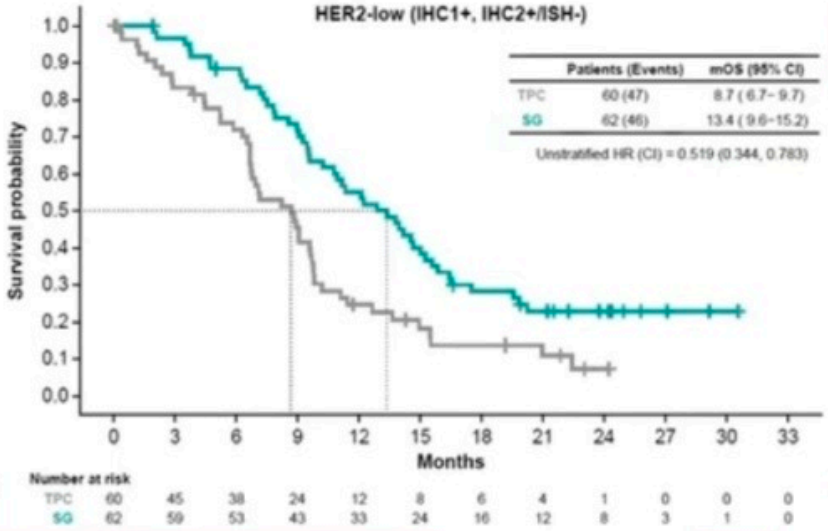
Phase 3 ASCENT: Survival Endpoints, HER2-low Population

Progression-free Survival



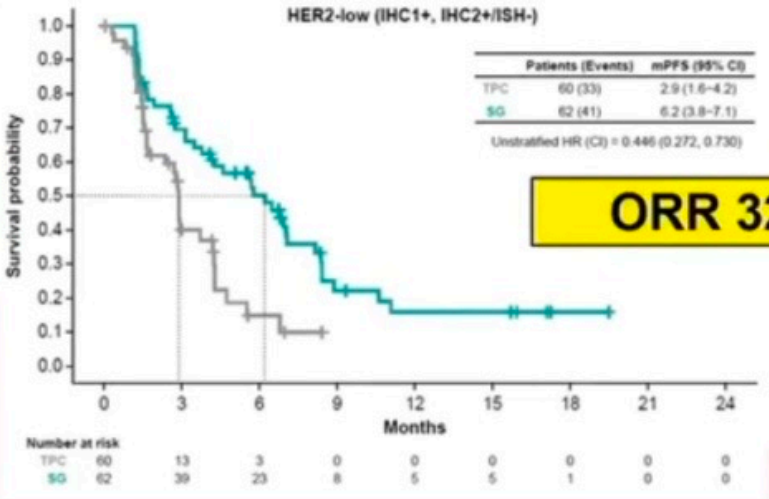
Overall Survival



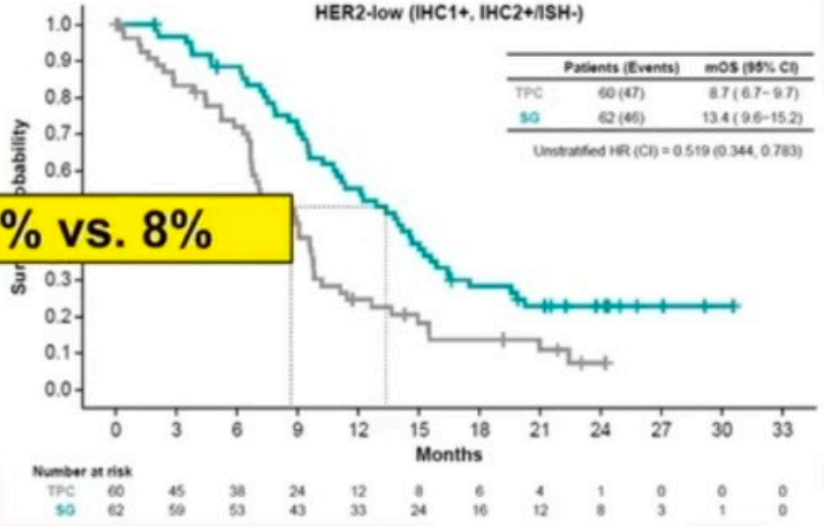
Bardia A, et al. *J Clin Oncol*. 2024 May 20;42(15):1738-1744.

Phase 3 ASCENT: Survival Endpoints, HER2-low Population

Progression-free Survival

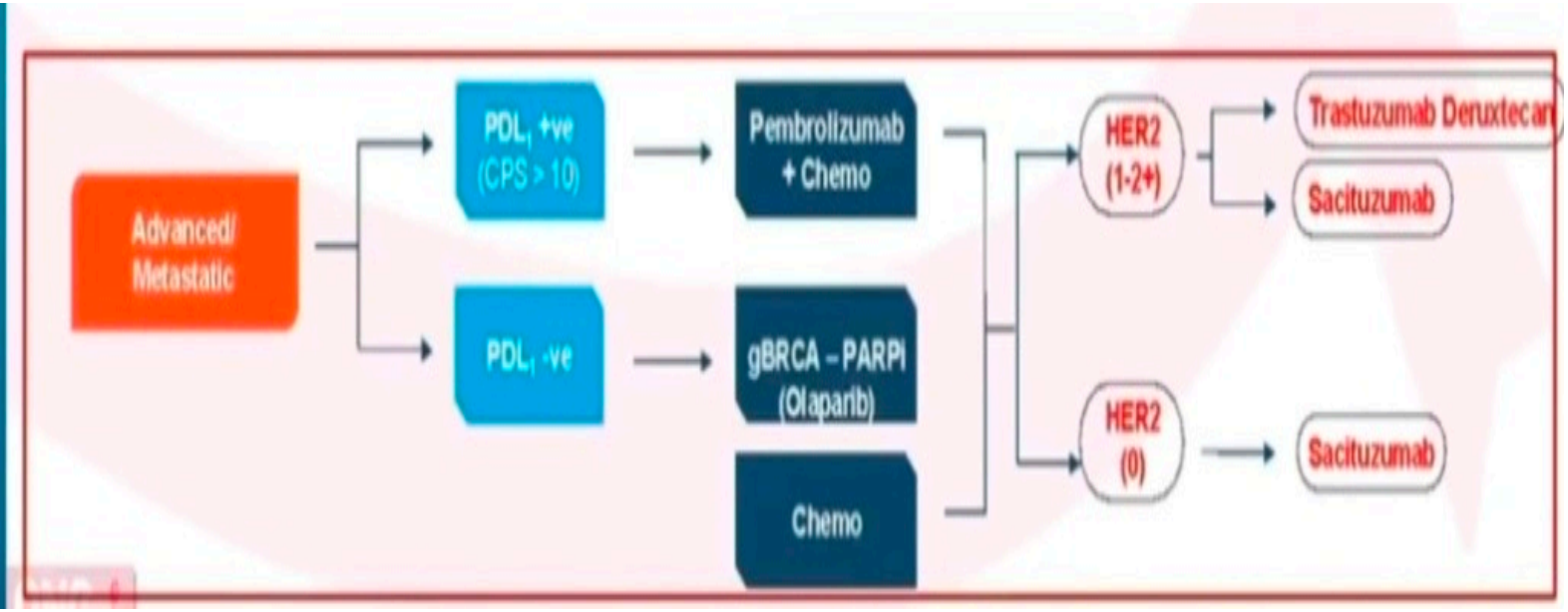


Overall Survival



ORR 32% vs. 8%

Bardia A, et al. *J Clin Oncol*. 2024 May 20;42(15):1738-1744.


Advanced/ Metastatic
PDL1 +ve (CPS > 10)
PDL1 -ve
Pembrolizumab + Chemo
gBRCA – PARPi (Olaparib)
Chemo
HER2 (1-2+)
HER2 (0)
Trastuzumab Deruxtecan
Sacituzumab
Sacituzumab

Treatment for mTNBC: Chemotherapeutic agents

- Taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents
- Single agent chemotherapy → Lower response rates and time to progression, but multi-agent chemo → more toxicity and no overall survival benefit.

Treatment for mTNBC: Case 5

A 46 year-old woman with a BRCA1 mutation transfers care to you. She breast cancer metastatic to her lungs, pleura, liver, and mediastinum, ER/PR/HER2 neg. Her disease has progressed on paclitaxel. PDL1 is negative. She feels well, has few symptoms, is still working. What do you recommend next?

A) Capecitabine
B) Olaparib
C) Ixabepilone
D) Atezolizumab + nab paclitaxel

Treatment for mTNBC: BRCA mutations

- OlympiAD trial (NEJM 2017): Among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy
- Median progression-free survival was 2.8 months longer, risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.
- FDA has approved olaparib and talazoparib in advanced breast, ovarian, fallopian tube, peritoneal, and pancreatic cancer for patients with germline BRCA mutations.

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

PARP inhibitors in *g*BRCA1/2 Mutant Advanced Breast Cancer

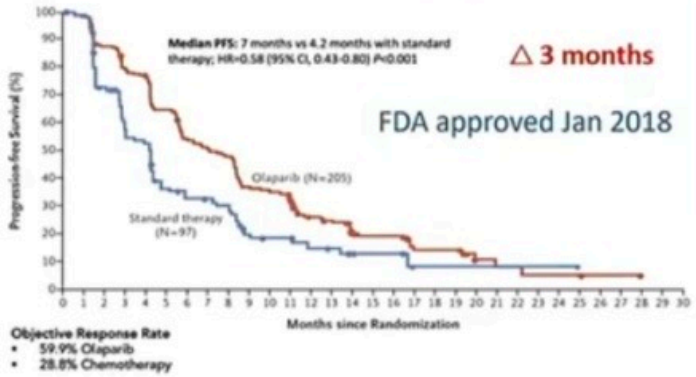
OlympiAD

*g*BRCA1/2, HER2-negative, Metastatic Breast Cancer
≤2 previous chemotherapy regimens
HR+ disease had to progress on at least 1 prior endocrine therapy

RANDOMIZED 2:1
n=302

- Olaparib 300 mg BID n=205
- MD Choice Chemotherapy* n=99

*Capecitabine, eribulin, or vinorelbine



Objective Response Rate
- 59.9% Olaparib
- 28.8% Chemotherapy

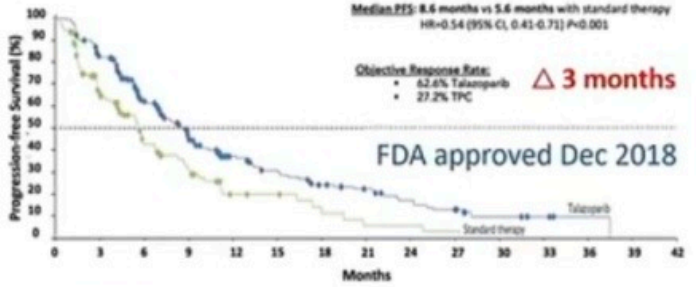
EMBRACA

*g*BRCA1/2, HER2-negative, Locally Advanced or Metastatic breast cancer
≤3 previous chemotherapy regimens
No limit on number of prior endocrine therapies

RANDOMIZED 2:1
N=431

- Talazoparib 1 mg daily n=287
- MD Choice Chemotherapy** n=144

**Capecitabine, eribulin, vinorelbine, or gemcitabine



Telli ML, et al. *SABCS 2023*. Robson M, et al. *N Engl J Med*.2017 Aug 10;377(6):523-533. Litton JK, et al. *N Engl J Med*. 2018 Aug 23;379(8):753-763.

PARP inhibitors in *g*BRCA1/2 Mutant Advanced Breast Cancer

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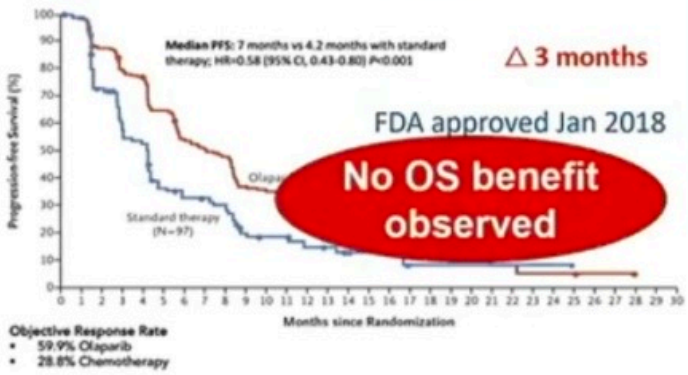

△ 3 months

FDA approved Jan 2018

No OS benefit observed

Objective Response Rate
- 59.9% Olaparib
- 28.8% Chemotherapy

EMBRACA

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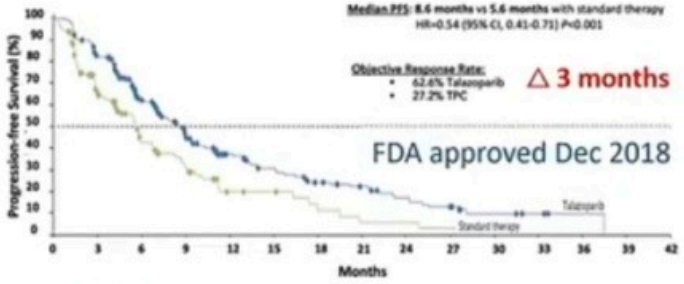
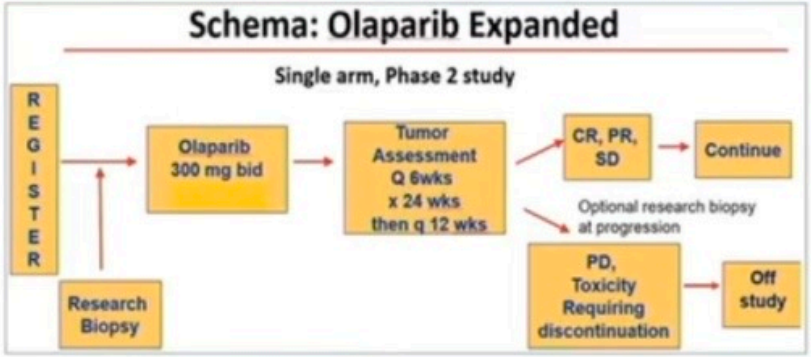


△ 3 months

FDA approved Dec 2018

Telli ML, et al. *SABCS 2023*. Robson M, et al. *N Engl J Med*.2017 Aug 10;377(6):523-533. Litton JK, et al. *N Engl J Med*. 2018 Aug 23;379(8):753-763.

TBCRC 048 Expansion Cohorts: gPALB2 and sBRCA1/2



gPALB2 N=24	
Best Response	Responses (rate, %)
Complete Response (CR)	1 (4%)
Partial Response (PR)	17 (71%)
Stable Disease (SD)	5 (21%)
Progressive Disease (PD)	1 (4%)
ORR = 75% (18/24, 80%-CI: 60%-86%)	
CBR (18 wks) = 83% (20/24, 90%-CI: 66%-94%)	

sBRCA1/2 N=30	
Best Response	Responses, (rate, %)
Complete Response (CR)	1 (3%)
Partial Response (PR)^	10 (33%)
Stable Disease (SD)	13 (43%)
Progressive Disease (PD)	6 (20%)
ORR = 37% (11/30, 80%-CI: 25%-50%)	
CBR (18 wks) = 53% (16/30, 90%-CI: 37%-69%)	

Other treatment considerations: Bone metastases

- In patients with bone metastatases, bisphosphonate treatment is associated with fewer skeletal-related events (SREs), fewer pathologic fractures, and lower need for radiation and surgery to treat pain.
- No impact on OS
- Dosing can be Q4 vs Q12 weeks w/ no significant difference in SREs in multiple trials. Reminder: Q6 months is nonmetastatic dosing for osteoporosis.

Role for surgery and radiation

- Multiple studies demonstrating no survival advantage for resection of breast tumor in setting of metastatic disease (exception: Turkish Federation MF07-01 trial, but groups were arguably not well balanced)
- Palliative role for surgery in case of painful breast tumors, impending fractures.
- Palliative role for radiation in pain control, stabilization of bone tumors, treatment of CNS disease

THANK YOU