Fred Hutch Cancer Center

Metastatic Breast Cancer

Sara Hurvitz, MD, FACP
Professor, Senior Vice President/Director Clinical Research Division
Professor, Head, Hematology/Oncology, UWSOM
Smith Family Endowed Chair in Women's Health
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Land Acknowledgement

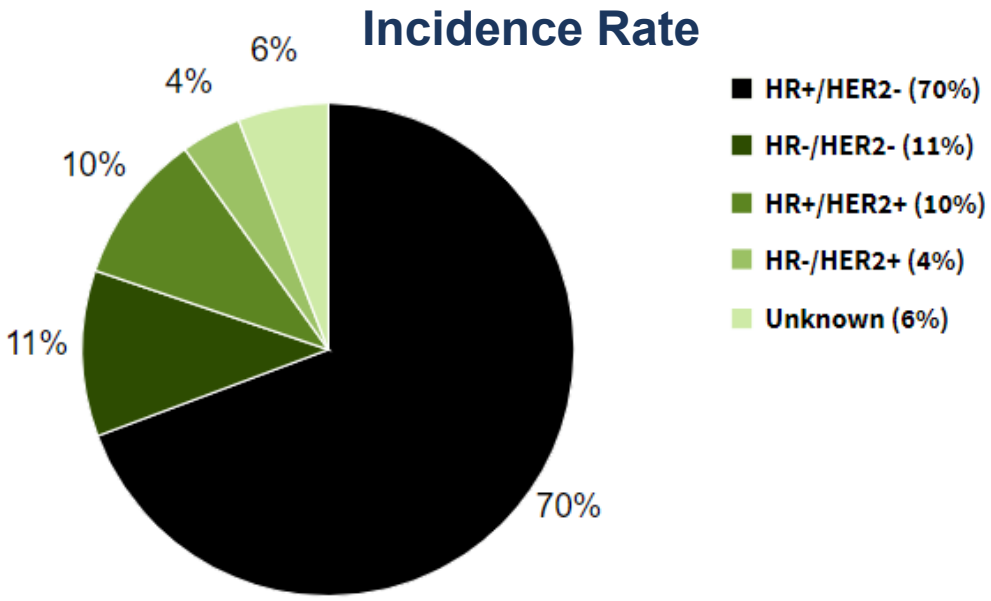
Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

Table of Contents

1. Background

Breast Cancer United States

- **Most common** type of cancer among females
- **13.1%** of all women will be diagnosed with breast cancer at some point in their lifetime



5-Year Relative Survival Percent

Subtype	Localized	Regional	Distant
HR+/HER2-	100.0%	90.5%	35.4%
HR-/HER2-	92.0%	66.8%	14.3%
HR+/HER2+	99.3%	90.4%	45.8%
HR-/HER2+	97.3%	84.2%	39.7%

SEER Cancer Stat Facts: Breast Cancer. NCI. Bethesda, MD. September 2024.
SEER Cancer Stat Facts: Female Breast Cancer Subtypes. NCI. Bethesda, MD. September 2024.

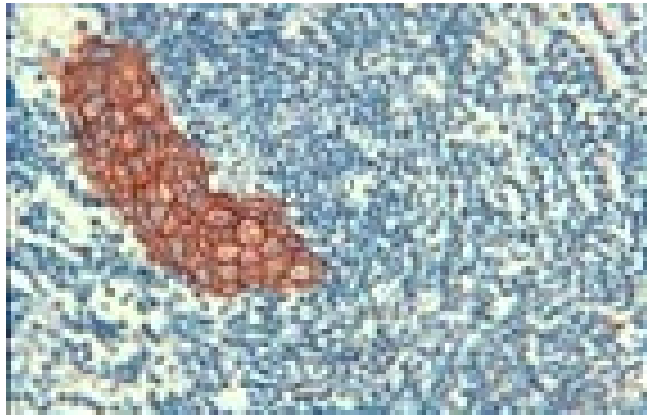
When metastatic disease is suspected:

- Tissue biopsy with biomarker assessment (ER, PR, HER2) and germline genetic testing (*BRCA1/2, PALB2)* is essential.
  - If recurrent HR+HER2-, testing for tumor *PIK3CA* mutation or *ESR1* mutation may be indicated (see below section on HR+)
- If bone metastases, start bone stabilizer (denosumab, pamidronate or q3 monthly zoledronic acid)
  - Ensure adequate renal function
  - Supplement calcium and vitamin D
  - Dental exam at baseline and every 6 months given risk of osteonecrosis of the jaw
    - Avoid bisphosphonate/RANKLi if dental extractions or implants (work with dentist to determine timing of intiation or resumption of bone stabilizer therapy)

2. HER2+ MBC

HER2 amplified breast cancer is associated with poor outcome

HER-2 Oncogene
Amplification



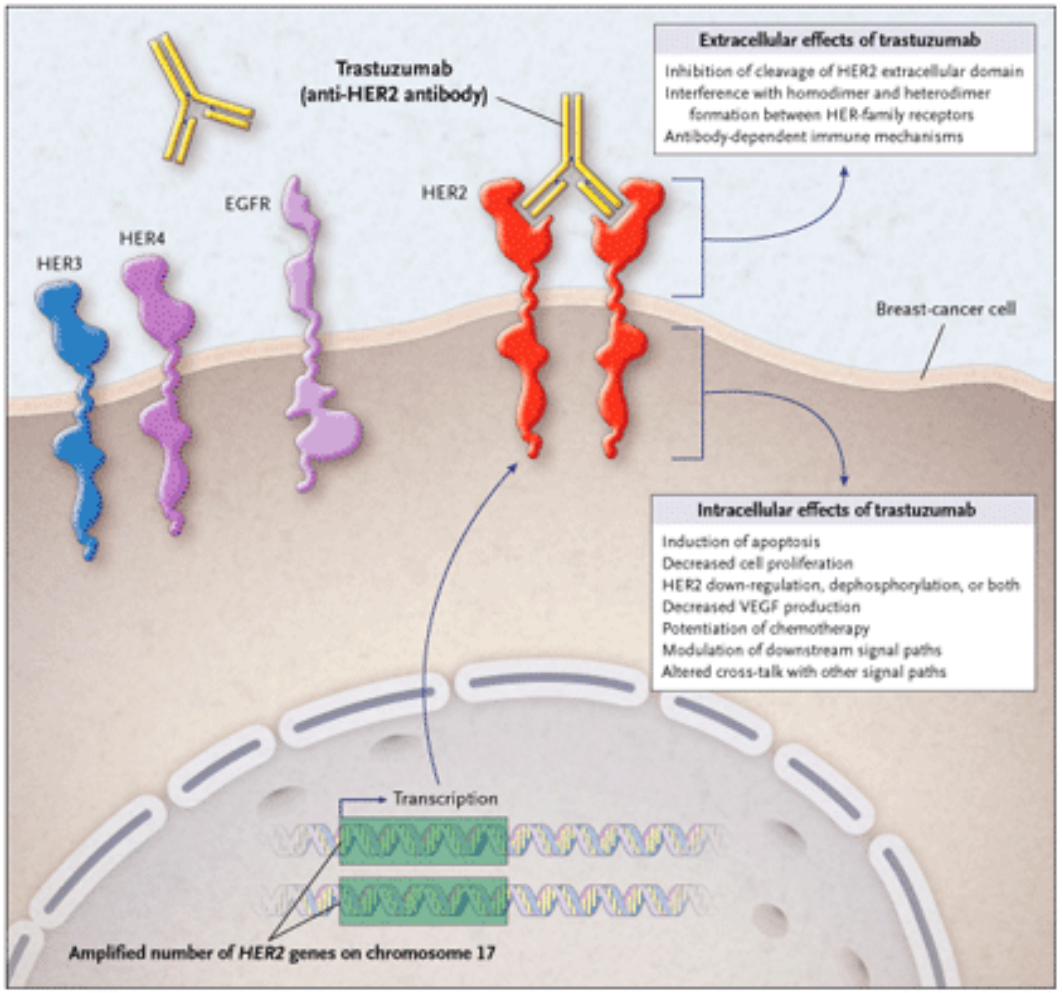
HER-2 Oncoprotein
Overexpression

Median Survival from First Diagnosis of Early-Stage LN+ BC

HER-2 overexpressing	3 yrs
HER-2 normal	6 - 7 yrs

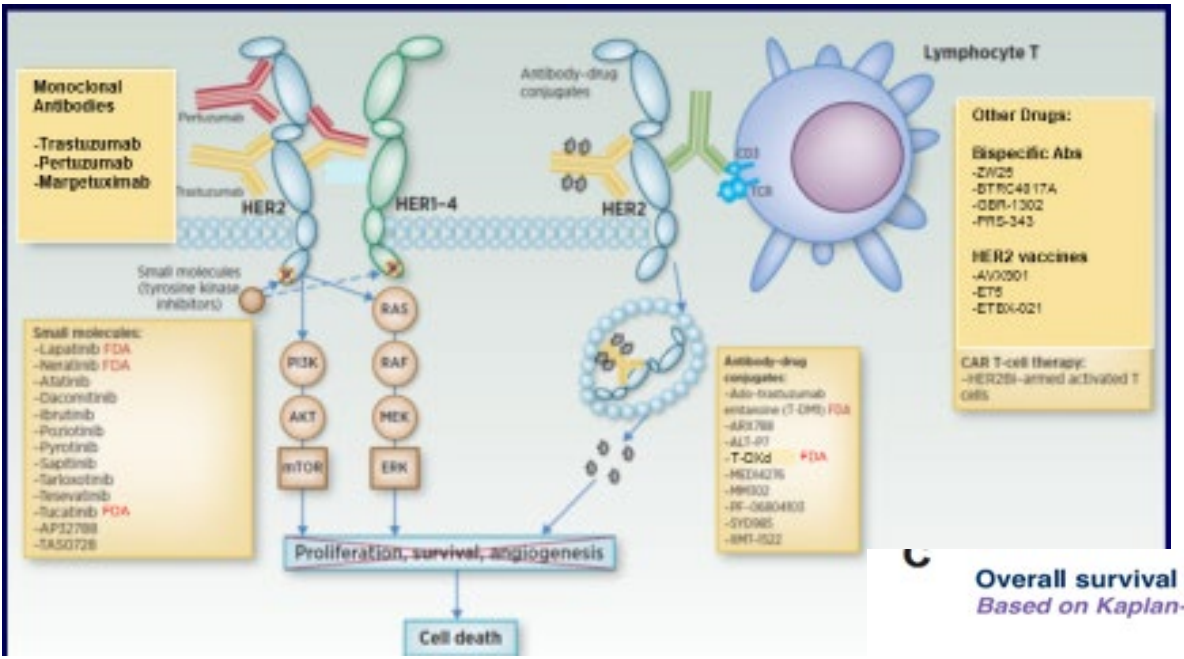
Slamon et al, *Science* 1987

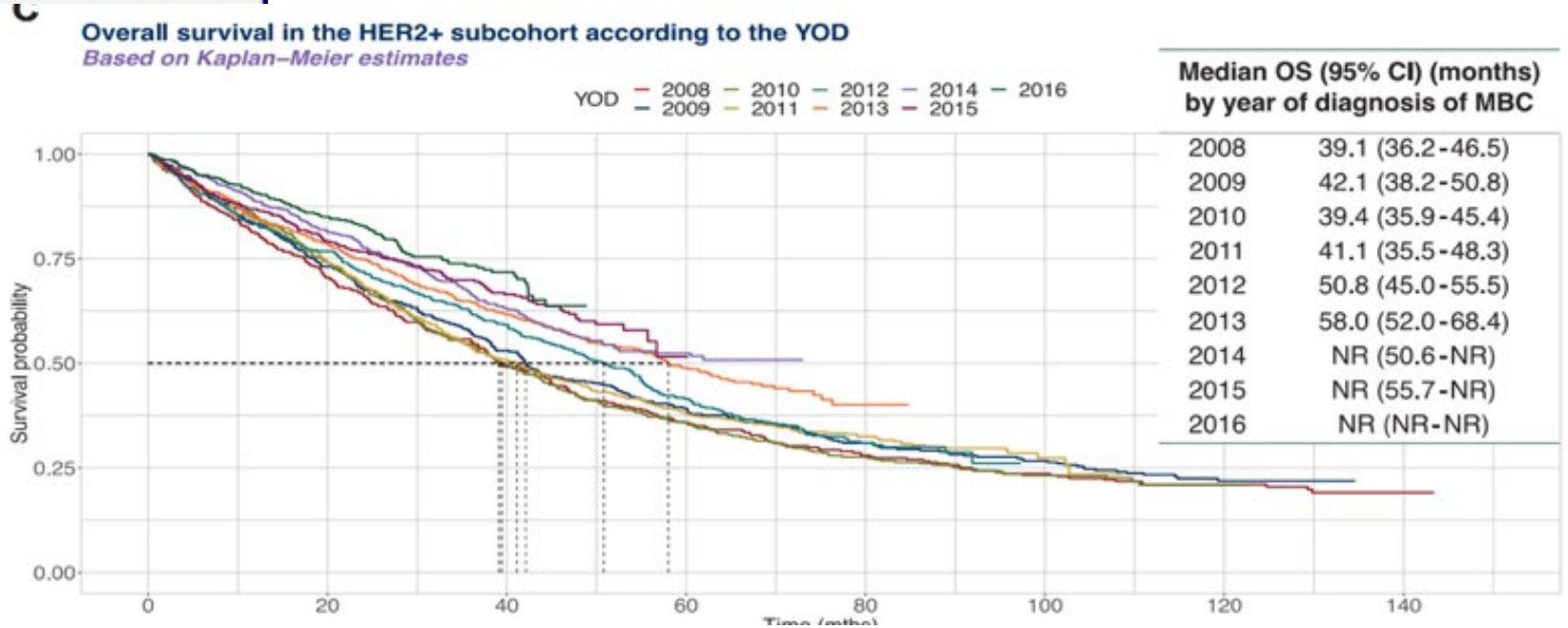
Trastuzumab Has Changed the Natural History of HER2+ Breast Cancer



Burstein H. *N Engl J Med.* 2005;353(16):1652-1654.

An Expanding Armementarium Is Improving Outcomes for HER2+ Disease





Bernstam FM, Clin Cancer Res 2019;25:2033
Grinda T, et al. ESMO Open. 2021;6:100114.

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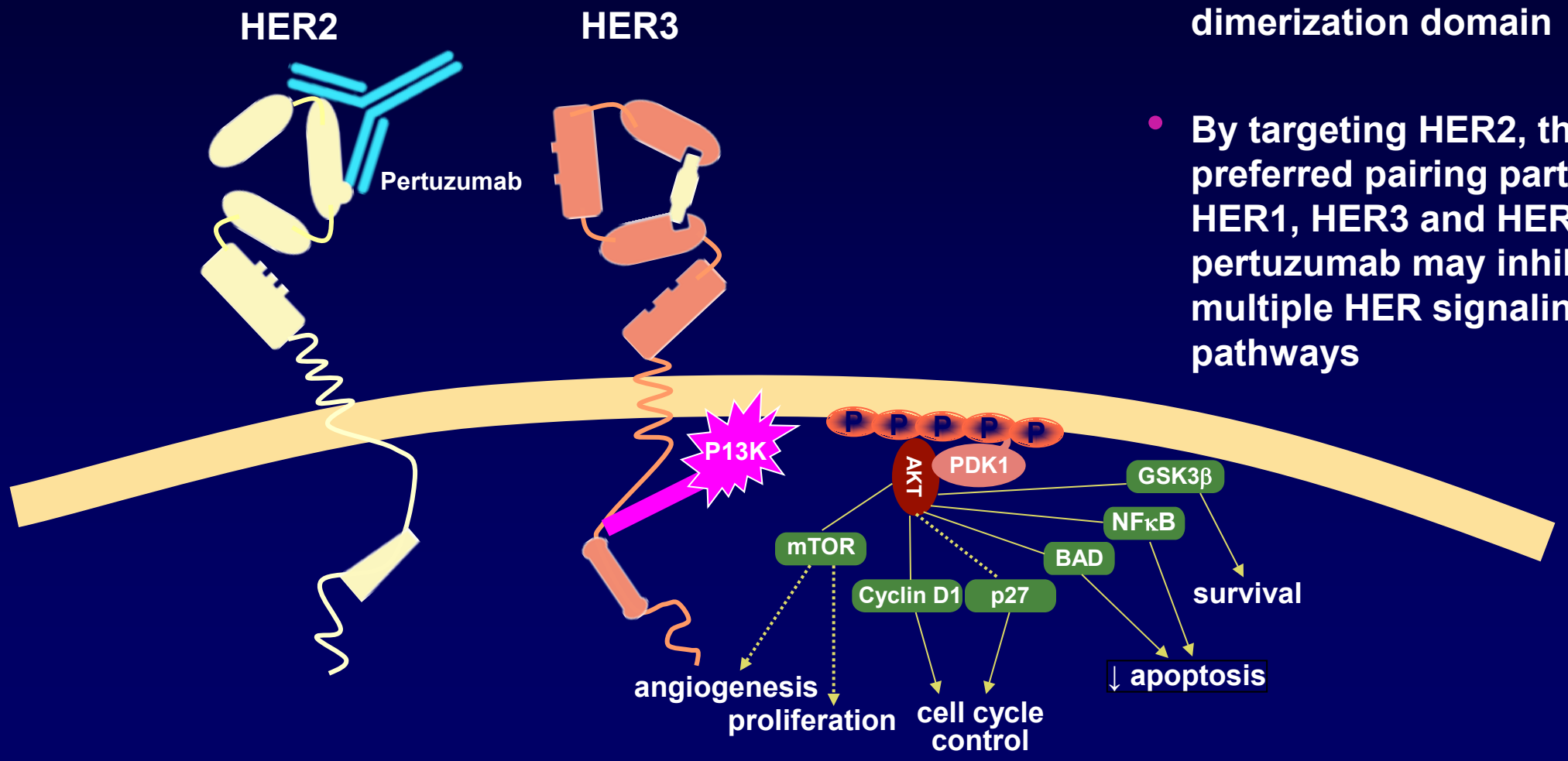
First Line Therapy HER2+

Trastuzumab + Pertuzumab + Taxane (“THP)

(docetaxel q3 weekly or paclitaxel weekly) induction for 4-8 cycles then maintenance trastuzumab/pertuzumab until progression of disease

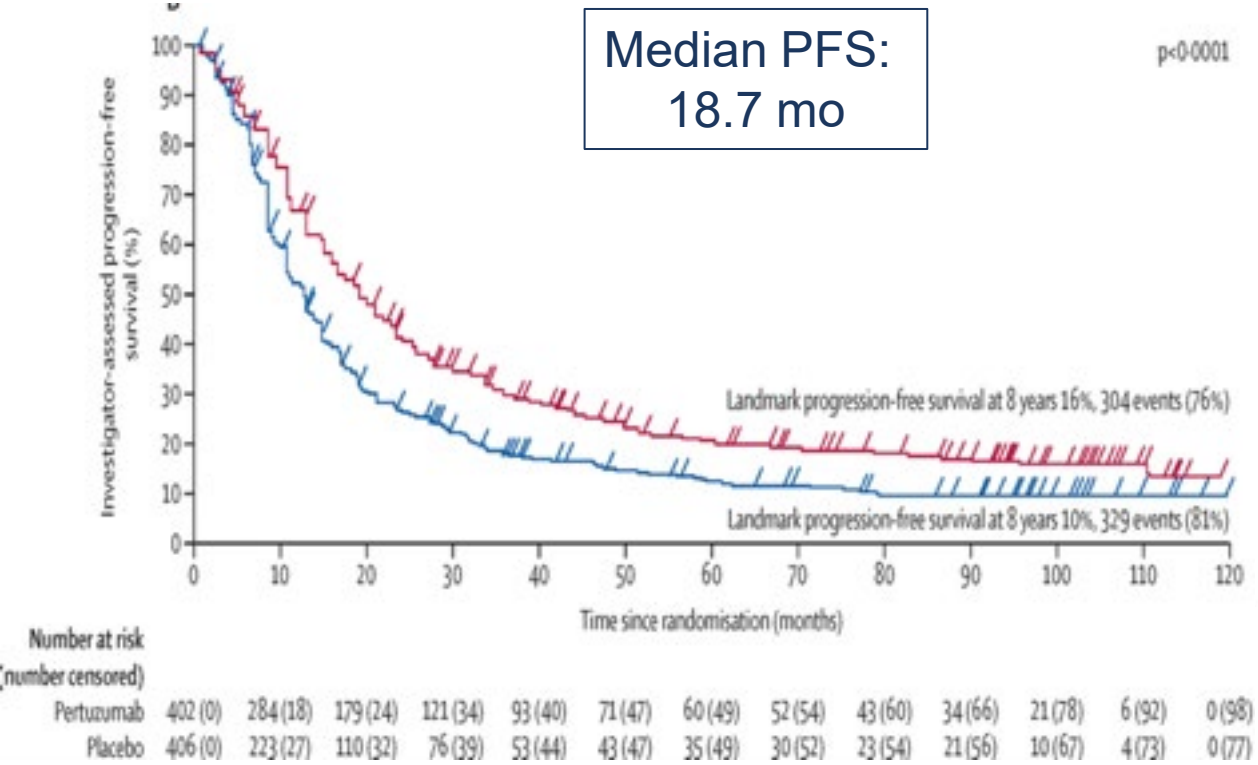
Pertuzumab: a HER2 dimerization inhibitor



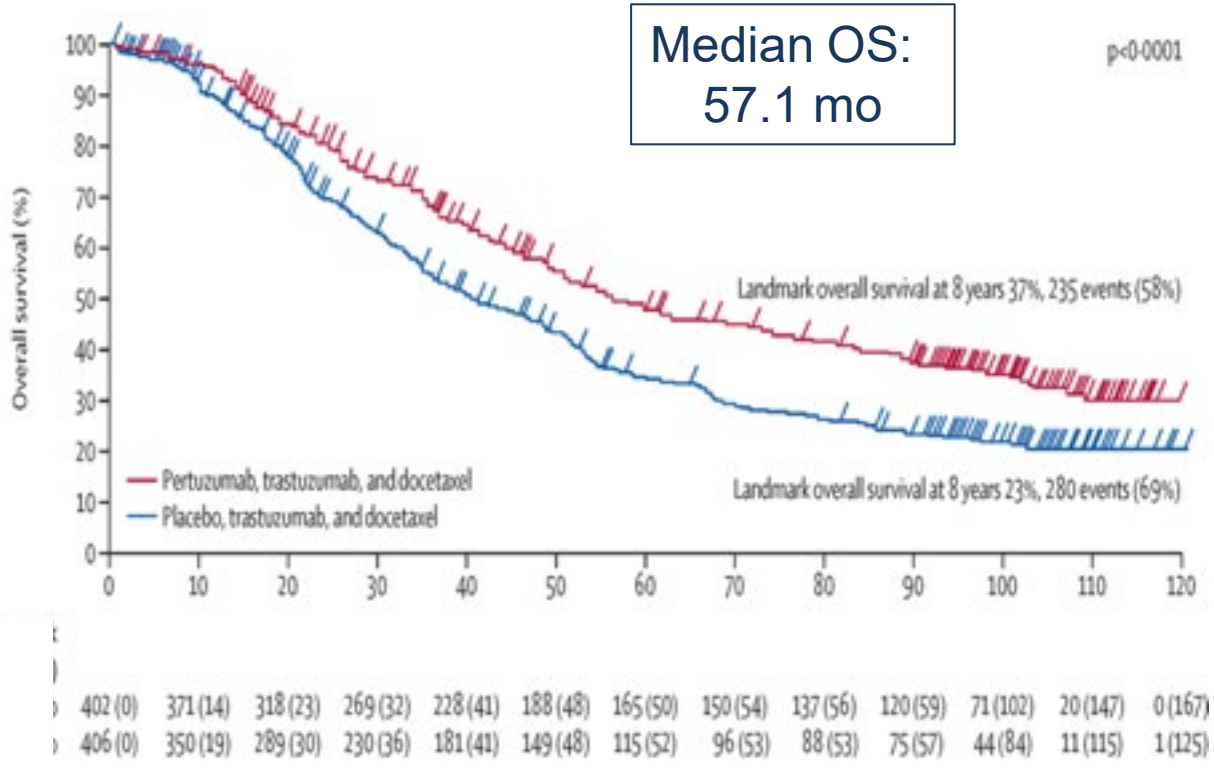
- A mechanism of action designed to bind to the HER dimerization domain
- By targeting HER2, the preferred pairing partner for HER1, HER3 and HER4, pertuzumab may inhibit multiple HER signaling pathways

CLEOPATRA End-of-Study Results:
Adding Pertuzumab to Taxane + Trastuzumab Improves PFS and OS
(median follow-up ~100 months)

Median PFS: 18.7 mo

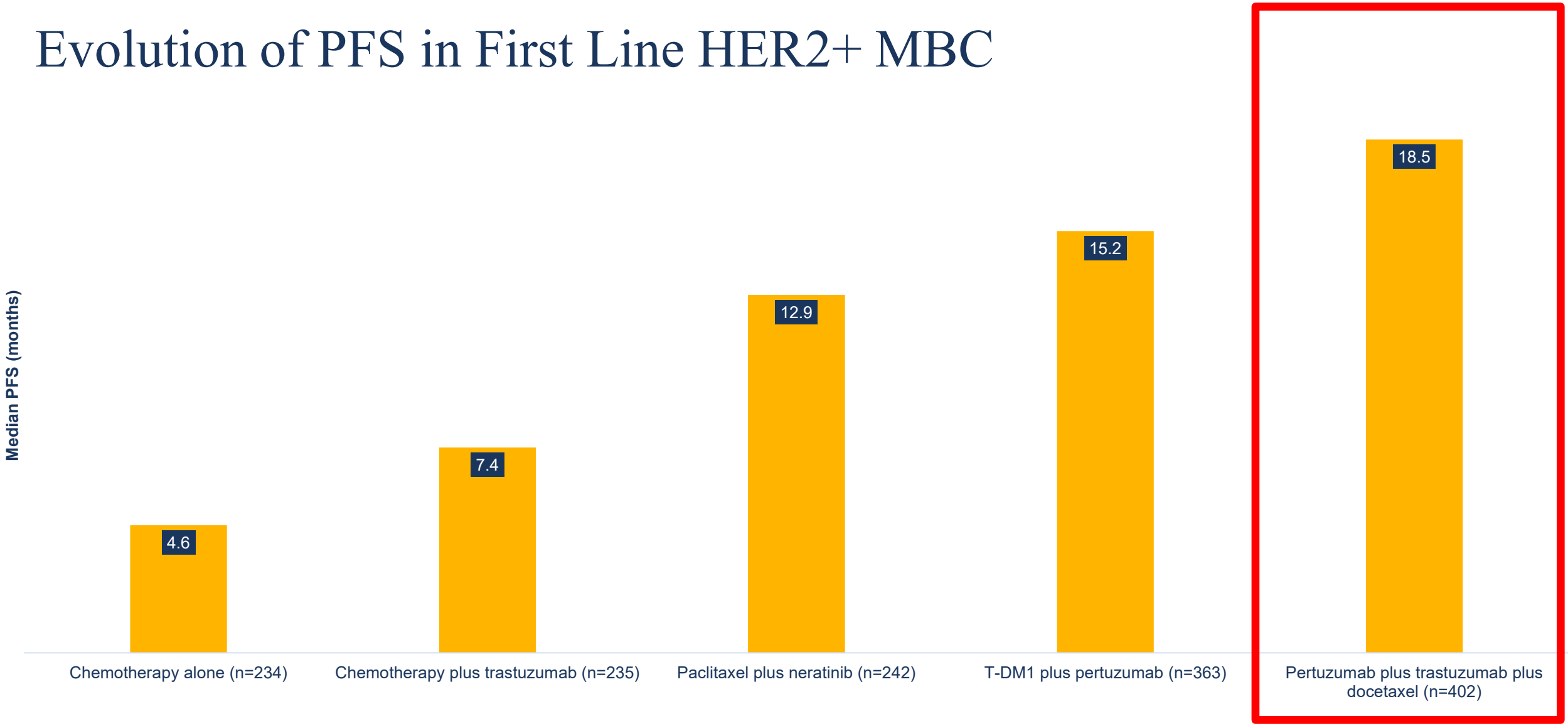


Median OS: 57.1 mo



Swain S, et al. Lancet Oncol. 2020;21:519-530.

Evolution of PFS in First Line HER2+ MBC

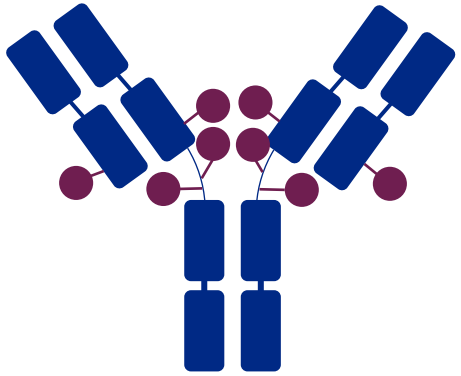


1L=first line; HER2=human epidermal growth factor receptor 2; PFS=progression-free survival; T-DM1=ado-trastuzumab emtansine.

1. Slamon DJ, et al. *N Engl J Med*. 2001;344:783-792. 2. Awada A, et al. *JAMA Oncol.* 2016;2:1557-1564. 3. Perez EA, et al. *J Clin Oncol.* 2017;35:141-148. 4. Baselga J, et al. *N Engl J Med.* 2012;366:109-119.

First Line Standard May Change Very Soon: Trastuzumab Deruxtecan (T-DXd): a Novel HER2 Antibody Drug Conjugate

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4]	ADC Attributes
Topoisomerase I inhibitor	**Payload MoA**
~8:1	**Drug-to-antibody ratio**
Yes	**Tumor-selective cleavable linker?**
Yes	**Evidence of bystander anti-tumor effect?**

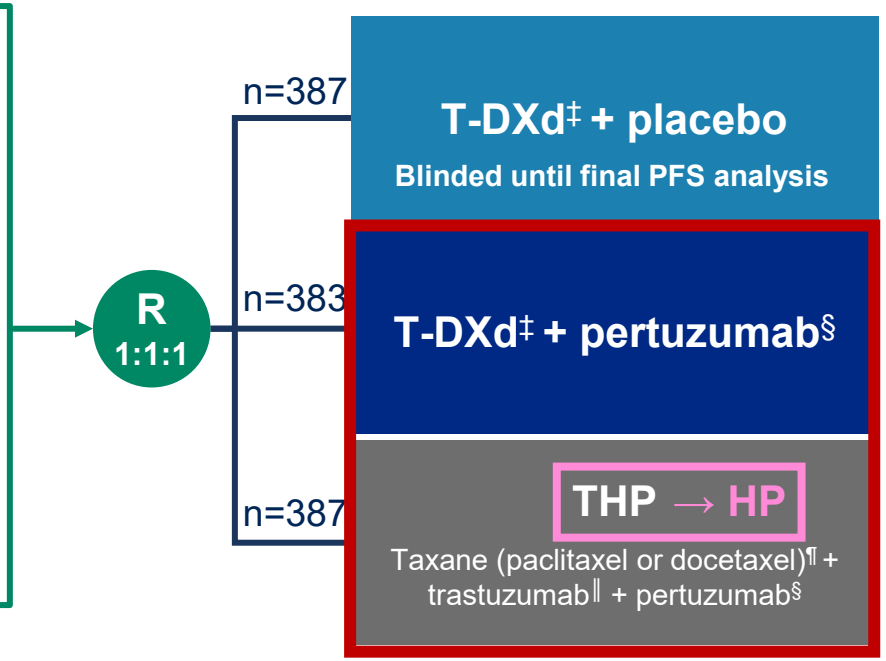
Abbreviations: ADC, antibody-drug conjugate; MoA, mechanism of action.

1. Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021

DESTINY-Breast09 – 1L HER2+ mBC

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/ adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

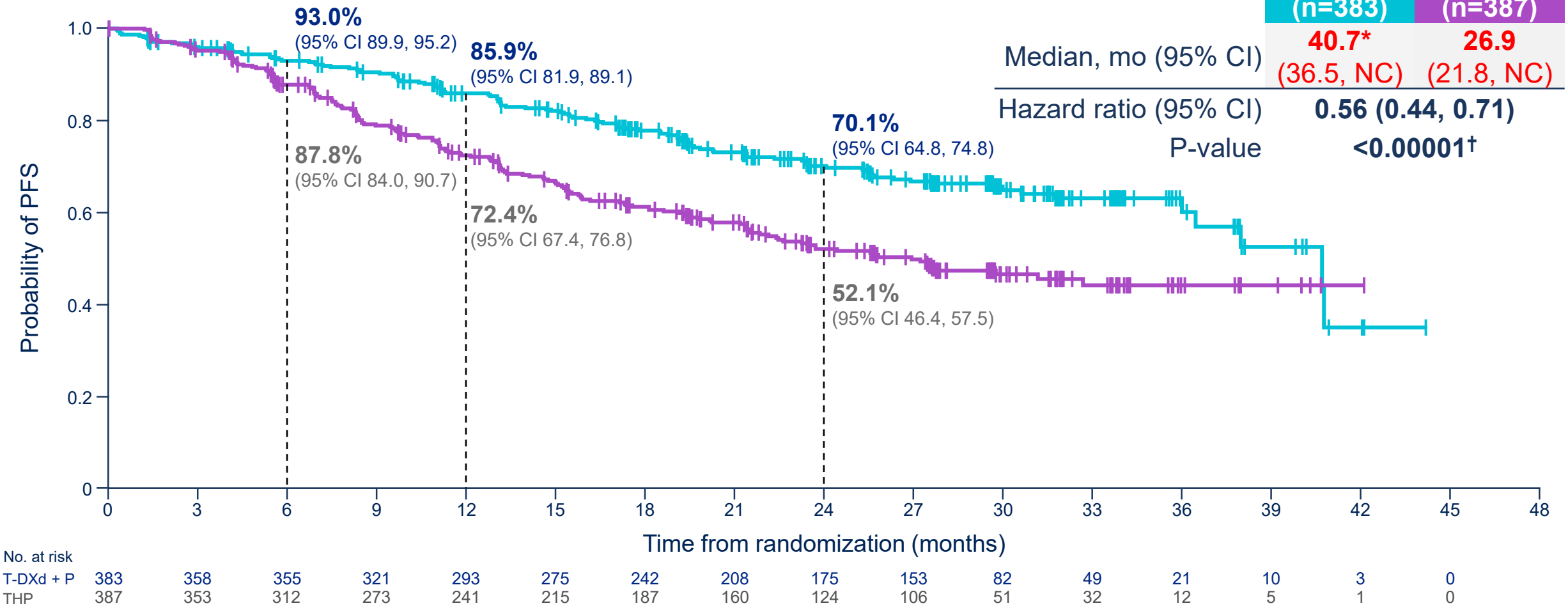
Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

- **Key participant characteristics:**
  - 51% de novo mBC; 54% HR+; ~82% IHC 3+
  - Of those initially diagnosed with ESB: ~ 80-85% received (neo)adjuvant chemo; **~ 58% trastuzumab**; **~15% pertuzumab**; **2% T-DM1**
  - Concurrent use of **ET in HR+**: **13.5% in T-DXd + P arm**; **38.3% in THP arm**

Tolaney S et al ASCO 2025

DB09 PFS (BICR): primary endpoint



	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001†	

No. at risk

T-DXd + P	383	358	355	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

DB09: T-DXd + Pertuzumab

- Median Progression Free Survival of 40.7 mos is historic!
  - THP in CLEOPATRA median PFS only 18.6 mos
  - THP in this study notably longer at 26 mos (endocrine therapy used during maintenance phase)
  - Likely will receive approval
  - But….

Is Frontline T-DXd/Pertuzumab necessary for everyone?

- Overall survival benefit not yet seen
- Unclear whether pertuzumab is adding anything to the T-DXd
- Very few patients crossed over so do not know if harming patients by waiting for 2nd line for T-DXd
- 16% of patients on CLEOPATRA were progression free at 8 years. Can we prospectively select those pts and treat them with THP—HP maintenance?
- Studies ongoing (DEMETHER) to evaluate induction T-DXd with maintenance HP strategy (Cortés J, *et al*. SABCS 2024; P5-03-11)
- Stay tuned!

Bernstam FM, Clin Cancer Res 2019;25:2033
Grinda T, et al. ESMO Open. 2021;6:100114.

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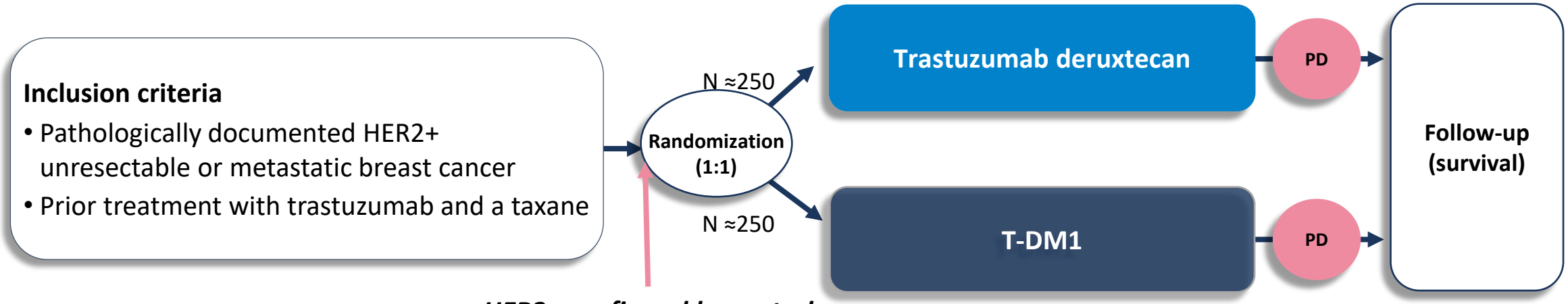
Second Line Therapy HER2+ (after trastuzumab/taxane)

T-DXd (if not yet received)
Tucatinib/trastuzumab/capecitabine (if T-DXd received, or if brain metastases)

DESTINY-Breast03: Trial Design
Trastuzumab Deruxtecan vs T-DM1

- Randomized open-label phase III trial

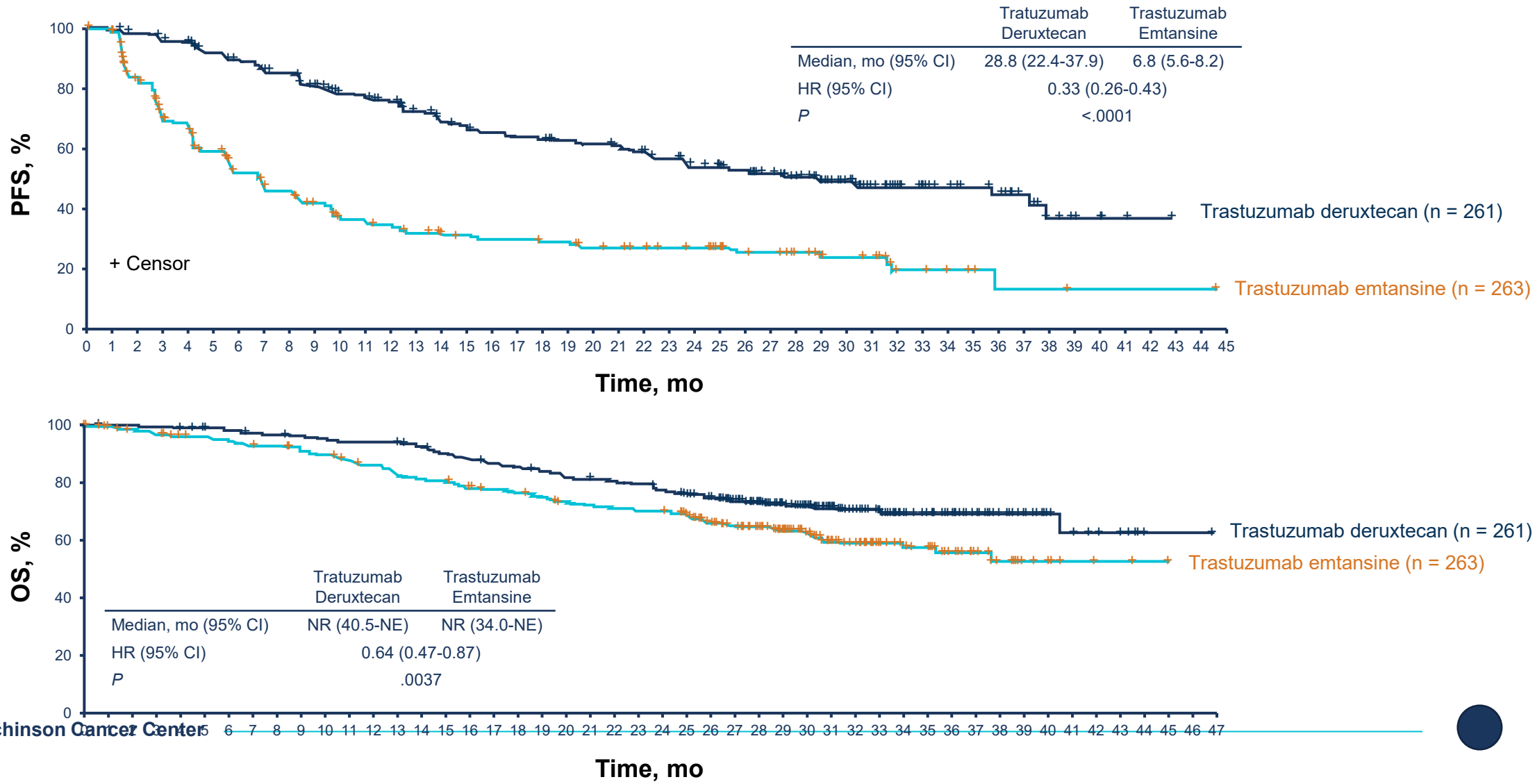


Prior therapy for MBC:
- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI

Endpoints
- Primary: PFS
- Secondary: OS, ORR, DOR

Abbreviations: DOR, duration of response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021.

DESTINY-Breast03: PFS and OS[1]



1. Hurvitz SA et al. *Lancet*. 2023;401:105-117.

DESTINY-Breast03: Adjudicated Drug-Related ILD/Pneumonitis[1]

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

- Interstitial lung disease occurs in 10-15% of patients treated with T-DXd. Deaths 1-3%
- Must hold therapy with grade 1 (asymptomatic, ground glass opacities/infiltrates on imaging) and do not restart until fully resolve. Consider steroids, pulm consult. If takes longer than one month to resolve, dose reduce
- Must permanently discontinue for any symptomatic ILD (and initiate steroids, involve pulmonology)

Hurvitz S et al. SABCS 2022. Abstract GS2-02.

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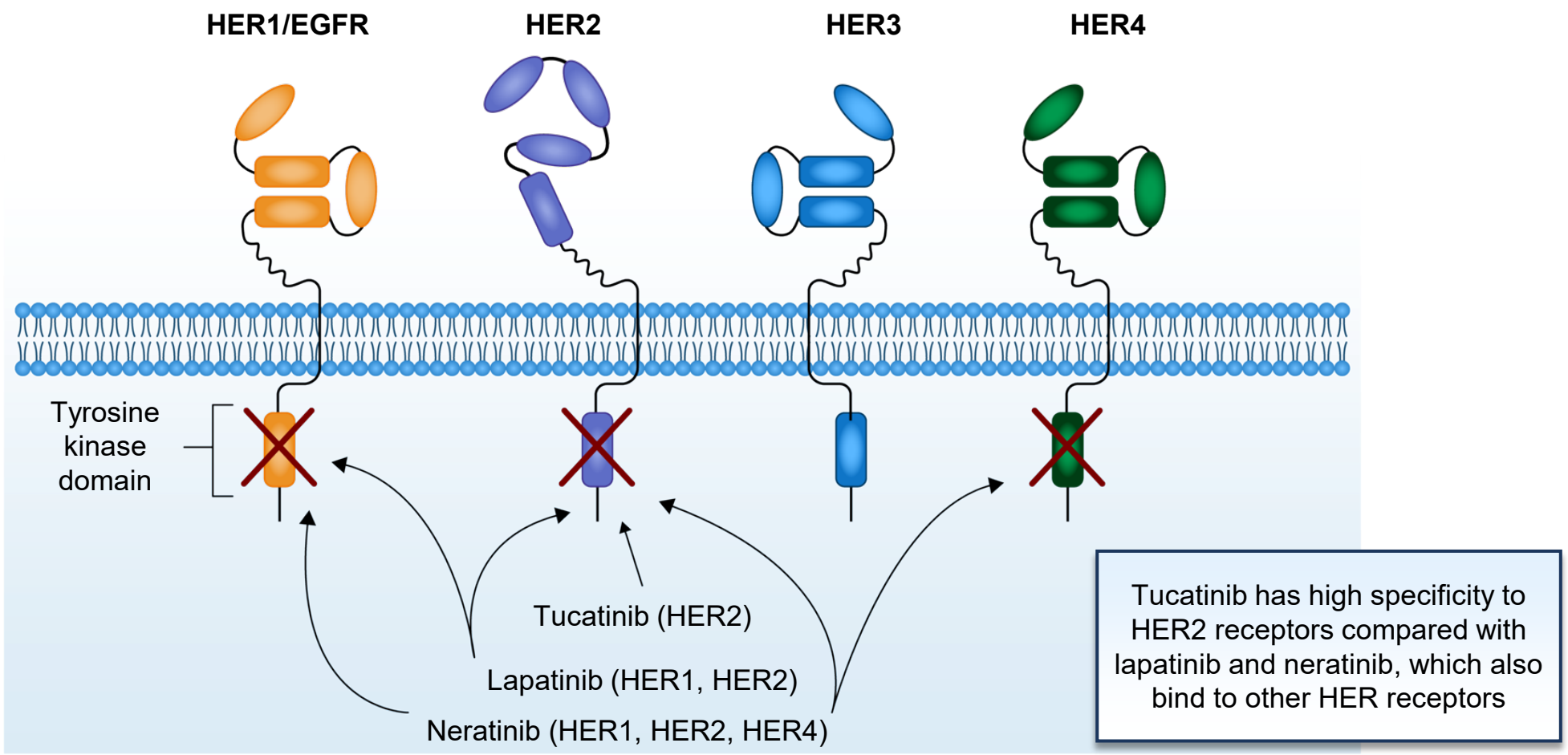
Third Line Therapy HER2+ and beyond

HER2-Targeted Tyrosine Kinase Inhibitors[1,2]



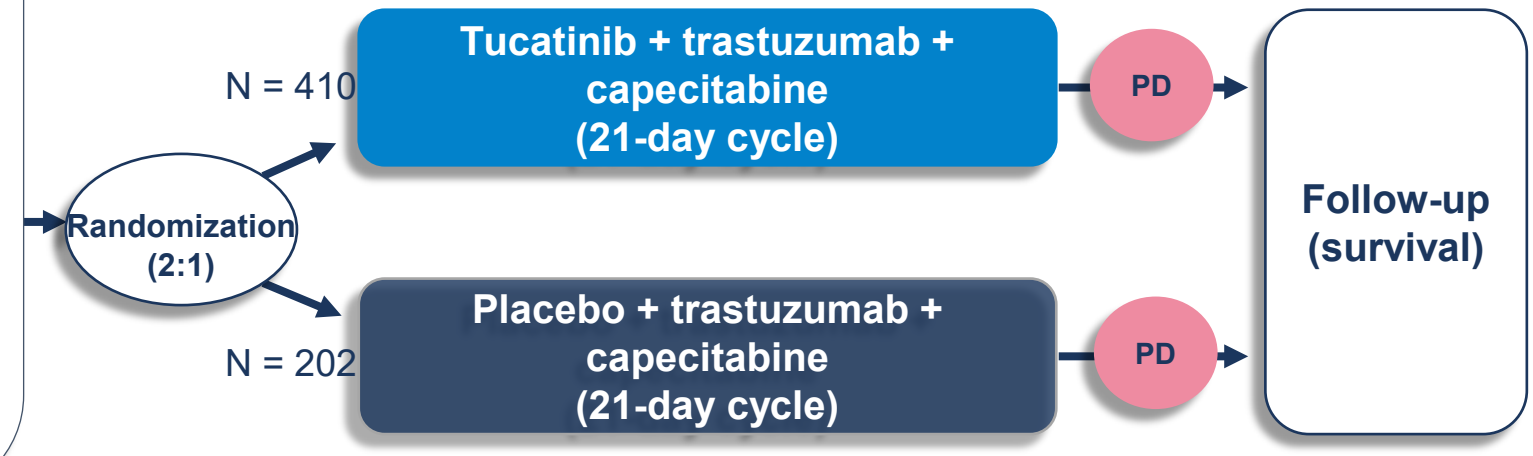
1. Dent SF, et al. Curr Oncol Rep. 2021;23:128. 2. Murthy R, et al. Lancet Oncol. 2018;19:880-888.

HER2CLIMB

Tucatinib + Trastuzumab + Capecitabine vs Placebo + Trastuzumab + Capecitabine

Inclusion criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- *Brain MRI at baseline*
  - *No evidence of brain metastases, or*
  - *Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy*



Stratification variables

- Presence of brain metastases (yes/no)
- ECOG status (0 or 1)
- Region of the world (US or Canada or rest of world)

Endpoints

- Primary: PFS (first 480 patients randomized)
- Secondary: OS (total population), PFS among patients with brain metastases, ORR

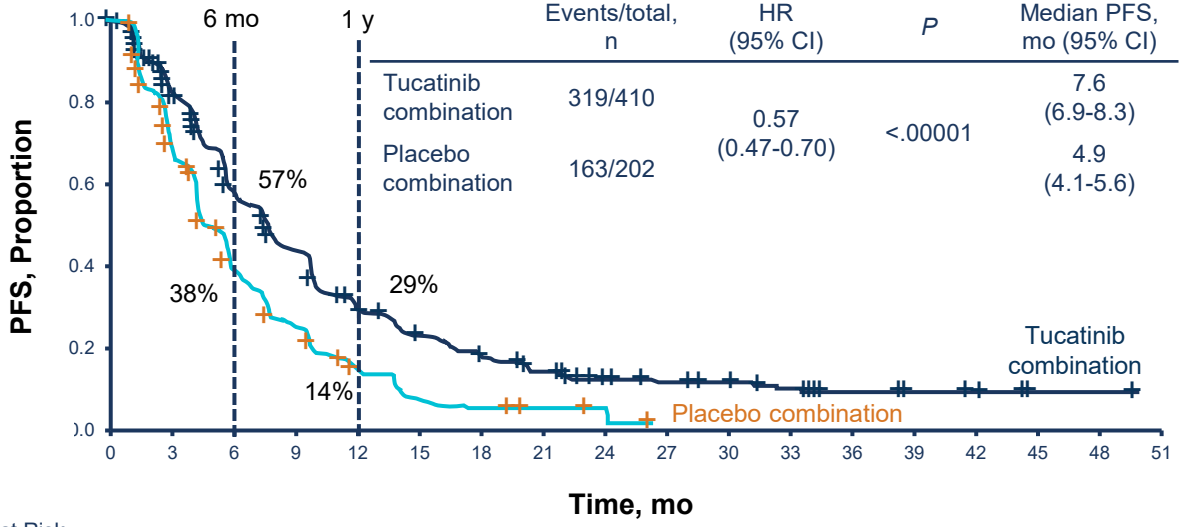
Notable baseline characteristic: *48% of patients had CNS metastases*

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

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

HER2CLIMB: PFS and OS[1] with tucatinib/capecitabine/trastuzumab

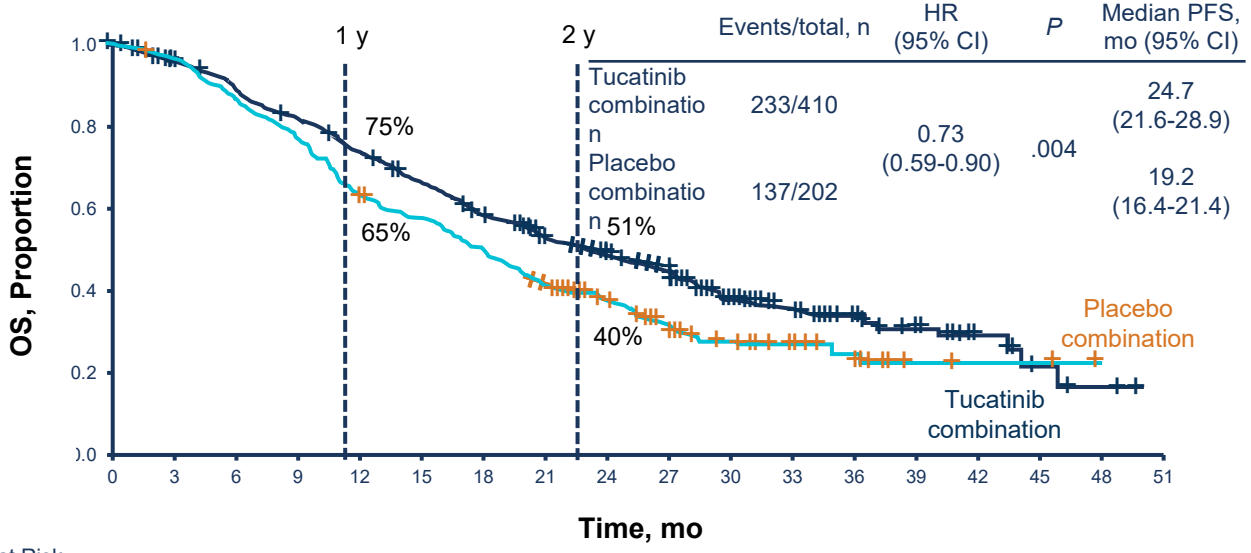
PFS



	Events/total, n	HR (95% CI)	*P*	Median PFS, mo (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<.00001	7.6 (6.9-8.3)
Placebo combination	163/202			4.9 (4.1-5.6)

No. at Risk																		
Tucatinib combination	410	303	205	154	99	77	59	44	28	24	20	14	9	5	4	1	1	0
Placebo combination	202	118	64	41	19	9	6	4	2	0	0	0	0	0	0	0	0	0

OS



	Events/total, n	HR (95% CI)	*P*	Median PFS, mo (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	.004	24.7 (21.6-28.9)
Placebo combination	137/202			19.2 (16.4-21.4)

No. at Risk																		
Tucatinib combination	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Placebo combination	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

1. Curigliano G et al. *Ann Oncol*. 2022;33:321-329.

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HER2+ Brain Metastases

Discussion: Should We Screen Asymptomatic Patients With HER2+ MBC for BMs?

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

”There are insufficient data to recommend for or against performing routine magnetic resonance imaging to screen for brain metastases; clinicians should have a low threshold for MRI of the brain because of the high incidence of brain metastases among patients with HER2+ advanced breast cancer.”

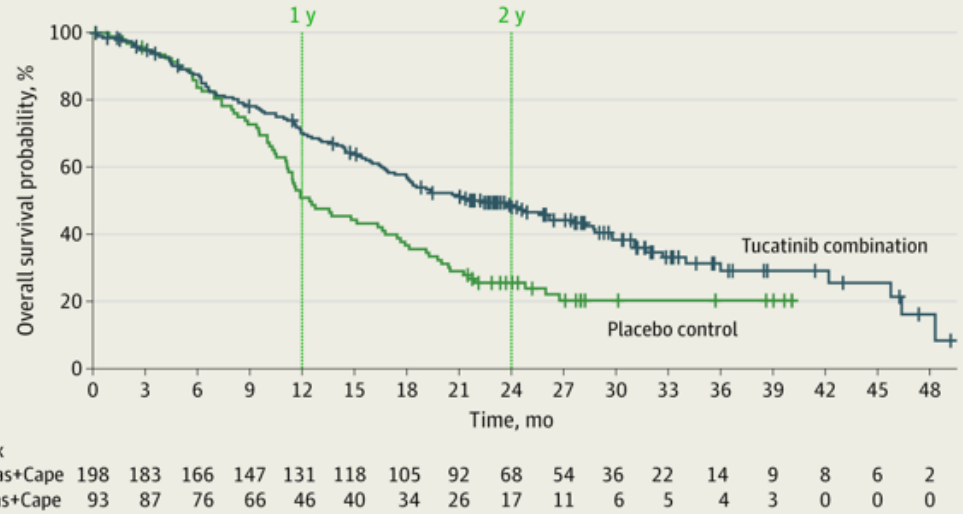
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

“Screening at diagnosis is potentially justified in HER2+ and TN MBC (EANO: IV, n/a; ESMO IV, B). This approach will result in a higher rate of detection of asymptomatic BM.”

Outcomes in HER2CLIMB in patients with CNS metastases

FINDINGS

Median OS was longer in the tucatinib-combination group compared with the placebo-combination group



Median OS:

21.6 mo (95% CI, 18.1-28.5 mo) in tucatinib-combination group

12.5 mo (95% CI, 11.2-16.9 mo) in placebo-combination group

Table. Confirmed Intracranial Responses in Patients With Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Intracranial response	Tucatinib combination (n = 55)[a]	Placebo combination (n = 20)[b]
Patients with objective response of confirmed complete response or partial response, No.	26	4
Confirmed ORR-IC, % (95% CI)	47.3 (33.7-61.2)	20.0 (5.7-43.7)
DOR-IC, median (95% CI), mo[c]	8.6 (5.5-10.3)	3.0 (3.0-10.3)

Abbreviations: DOR-IC, duration of intracranial response; ORR-IC, intracranial objective response rate.

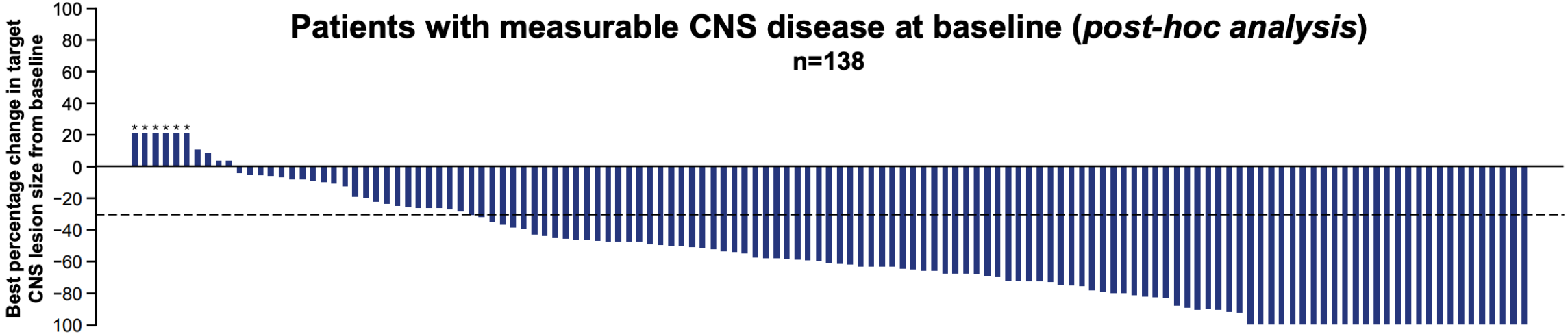
[a] Tucatinib, trastuzumab, and capecitabine.

[b] Placebo, trastuzumab, and capecitabine.

[c] Calculated with the complementary log-log transformation method.

Lin, et al. JAMA Oncol. 2023;9(2):197-205. doi:10.1001/jamaoncol.2022.5610

DESTINY-Breast12: T-DXd in Patients with CNS metastases Baseline BMs: CNS ORR[1]



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

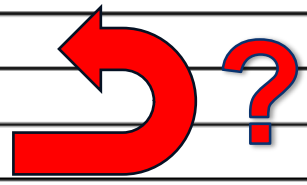
T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Dashed line indicates a 30% decrease in target tumor size (PR). *Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD.

1. Lin N et al. ESMO 2024. Abstract LBA18.

Summary: Standard for HER2+ MBC

HR-Positive or -Negative and HER2-Positive[m]	
See BINV-Q (1) for Considerations for systemic HER2-targeted therapy.	
Setting	**Regimen**
First Line[n]	Pertuzumab + trastuzumab + docetaxel (category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[o]	Fam-trastuzumab deruxtecan-nxki[n] (category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[o] (category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[p]
Fourth Line and Beyond (optimal sequence is not known)[q]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[r,s]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Abemaciclib in combination with fulvestrant and trastuzumab (for HR+ only) (category 2B)
	Targeted Therapy and emerging biomarker Options BINV-Q (7) and BINV-Q (8)



HER2+ Brain Metastases: NCCN Guidelines v2.2025

- **HER2 positive**
  - **Preferred**
    - **Tucatinib + trastuzumab + capecitabine (category 1) if previously treated with ≥1 regimen[6]**
    - **Fam-trastuzumab deruxtecan-nxki if previously treated with ≥1 regimen[7,8]**
  - **Other Recommended**
    - **Ado-trastuzumab emtansine (T-DM1)[9]**
    - **Neratinib and T-DM1[10]**
    - **Capecitabine + lapatinib[11,12]**
    - **Capecitabine + neratinib[13,14]**
    - **Pertuzumab and high-dose trastuzumab[d,15]**
    - **Paclitaxel + neratinib (category 2B)[16]**

Summary: Standard for HER2+ MBC

First Line

Trastuzumab + pertuzumab + taxane

CLEOPATRA

- Continue HP after induction
- HR+: Consider addition of palbociclib and endocrine therapy to HP (PATINA trial)

Second Line

Trastuzumab deruxtecan (T-DXd)

DB03

or

Tucatinib + trastuzumab + capecitabine

HER2CLIMB

Factors include extracranial disease burden, intracranial disease burden, comorbidities, patient preference

Third Line

Tucatinib + trastuzumab + capecitabine

HER2CLIMB

or

Trastuzumab deruxtecan

DB02/03

or

Trastuzumab emtansine (T-DM1)

EMILIA, TH3RESA

Late Line Options for HER2+ MBC: "Dealer's Choice"

Fourth Line +

- Trastuzumab emtansine (T-DM1) — TH3RESA
- Margetuximab + chemo — SOPHIA
- Neratinib + capecitabine — NALA
- Trastuzumab + chemo
- Trastuzumab + lapatinib — EGF104900

Many possible agents, including

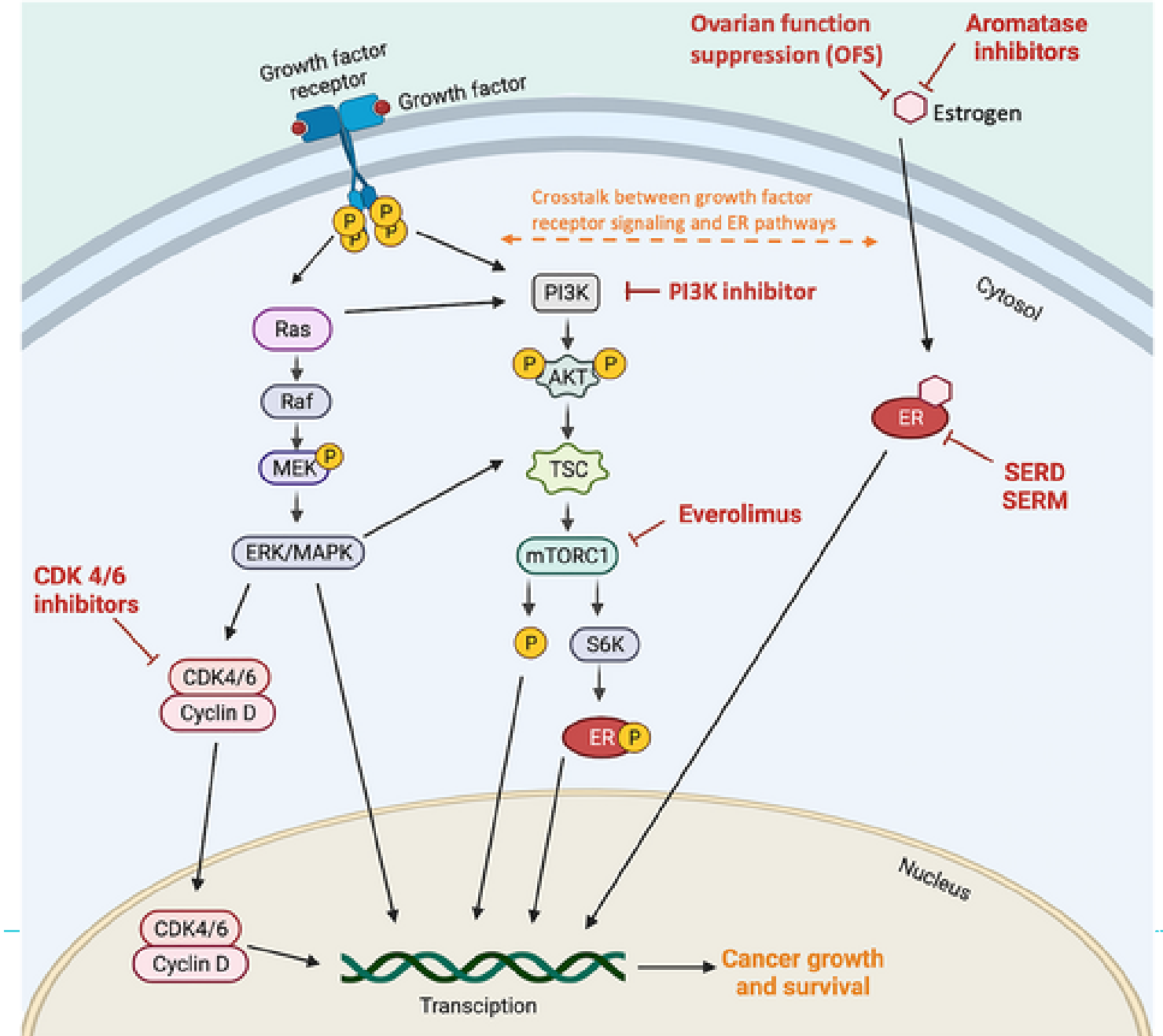
- Vinorelbine
- Eribulin
- Gemcitabine
- Doxil
- Carboplatin

Special consideration in HR+/HER2+:
fulvestrant/abema/trastuzumab

Or tucatinib/capecitabine/trastuzumab, or T-DXd if not already received

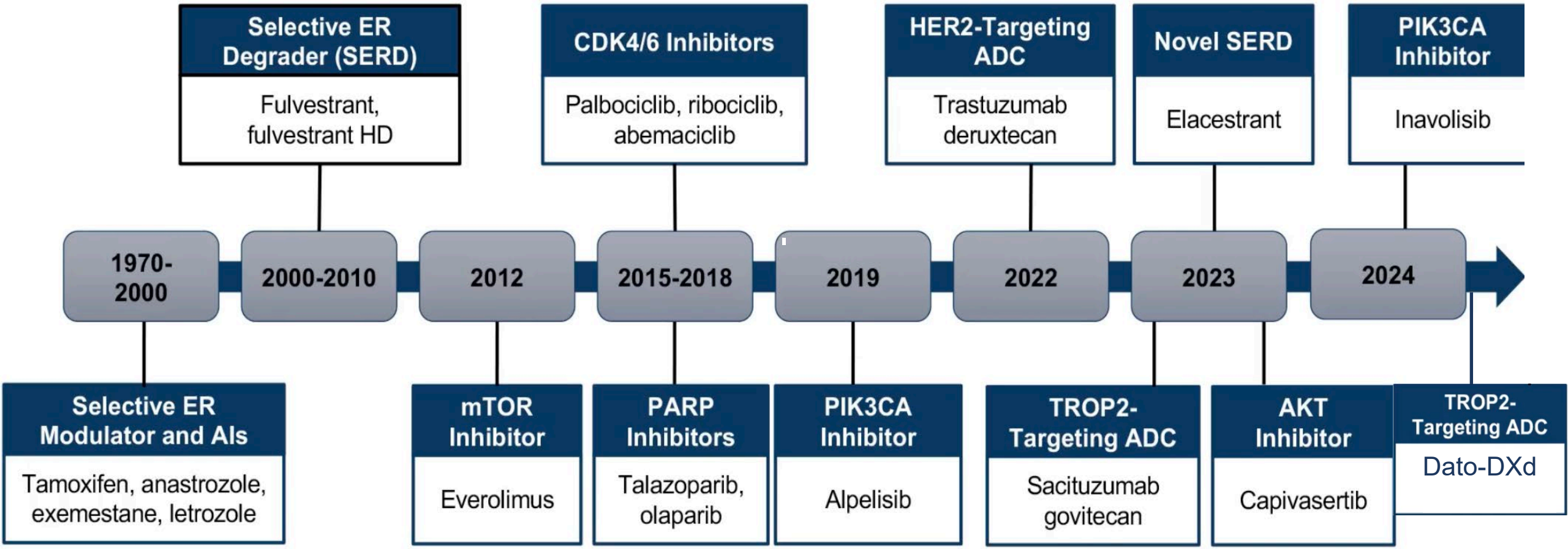
3. Hormone Receptor Positive (HR+), HER2- MBC

Pathways to Target in HR+ Breast Cancer



Huppert LA, et al. *CA*. 2023; 73(5):480-515.

Evolving Treatment Landscape of HR+, HER2- Advanced Breast Cancer



Treatment Recommendations
HR+/HER2- mBC

First Line

- **CDK4/6 inhibitor + ET**
- Inavolisib/palbociclib/fulvestrant**

***If recurrence on/within 12 months of adjuvant AI treatment AND tumor PIK3CA mutation AND acceptable baseline glucose parameters*

Subsequent Lines

- Endocrine-Targeted Therapies
  - CDK4/6 inhibitor + fulvestrant (if not used first-line)
  - Everolimus + ET
  - Targeted therapy (*PI3K*/*AKT1*/mTOR, *PTEN*, *ESR1*, etc.)
  - PARP inhibitor (if *BRCA1/2* mutation)
  - Endocrine monotherapy (fulvestrant, aromatase inhibitor, or tamoxifen)

Burstein HJ, et al. *J Clin Oncol*. 2024;42(12):1450-53
NCCN. Breast Cancer (version 1. 2025).

HR: hormone receptor
HER2-: human epidermal growth factor receptor 2
ET: endocrine therapy
CDK4/6 inhibitor: Cyclin-dependent kinase 4 and 6 inhibitor
ESR1: estrogen receptor 1

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First-Line

Cyclin Dependent Kinase 4/6 inhibitor plus endocrine therapy

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	***No***
MONALEESA-2	**Ribociclib**	1st Line/AI	Post	0.57	Yes	**0.76**	**Yes**
MONALEESA-7*	**Ribociclib**	1st Line/AI or Tam	Pre/Peri	0.55	Yes	**0.70**	**Yes**
MONARCH-3	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	***Possibly***
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2	**Abemaciclib**	2nd Line/Fulv	Pre/Post	0.55	Yes	**0.78**	**Yes**
MONALEESA-3	**Ribociclib**	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	**0.72**	**Yes**

- PALOMA-2: Finn R, et. al. New Engl J Med 2016; Rugo H, et al. Breast Cancer Res Treat, 2019. Finn R et al. ASCO 2022 LBA1003
- MONALEESA-2: Hortobagyi G, et al. New Engl J Med 2016; Hortobagyi G, et al. Ann Oncol 2018.
- MONALEESA-7: Tripathy D, et al. Ann Oncol 2018; Im S-A, et al New Engl J Med 2019. [Note PFS/OS data reported for approved AI subset]
- MONARCH-3: Goetz M, et al. J Clin Oncol 2017; Johnson S, et al. npj Breast Cancer 2019. Goetz et al ESMO 2022
- PALOMA-3: Turner N, et al. New Engl J Med 2015; Cristofanilli M, et al. Lancet Oncol 2016; Turner N, et al New Engl J Med 2018.
- MONARCH-2: Sledge G, et al. J Clin Oncol. Sledge G, et al. JAMA Oncol 2019.
- MONALEESA-3: Slamon D, et al. J Clin Oncol 2018; Slamon D, et al New Engl J Med 2020.

Should (young) patients with highly symptomatic visceral disease receive chemo instead of CDK4/6i?

YES!!

RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

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

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

RIGHT Choice: Ribociclib better than chemotherapy!

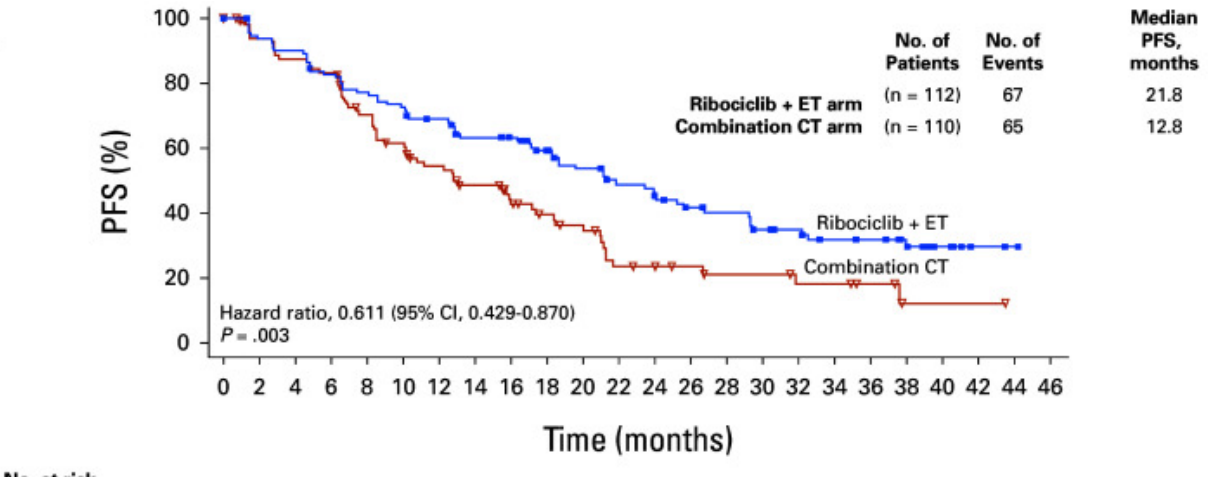

TABLE 2. ORR and CBR (full analysis set)

Outcome Measures	Ribociclib + ET (n = 112)[a]	Combination CT (n = 110)[a]
Best overall response		
Complete response	7 (6.3)	3 (2.7)
Partial response	67 (59.8)	65 (59.1)
Stable disease	27 (24.1)	20 (18.2)
Progressive disease	9 (8.0)	6 (5.5)
Unknown	2 (1.8)	16 (14.5)
ORR,[b] No. (%) 95% CI	74 (66.1) 56.5 to 74.7	68 (61.8) 52.1 to 70.9
CBR,[c] No. (%) 95% CI	91 (81.3) 72.8 to 88.0	82 (74.5) 65.4 to 82.4

Lu YS, et al. J Clin Oncol. 2024

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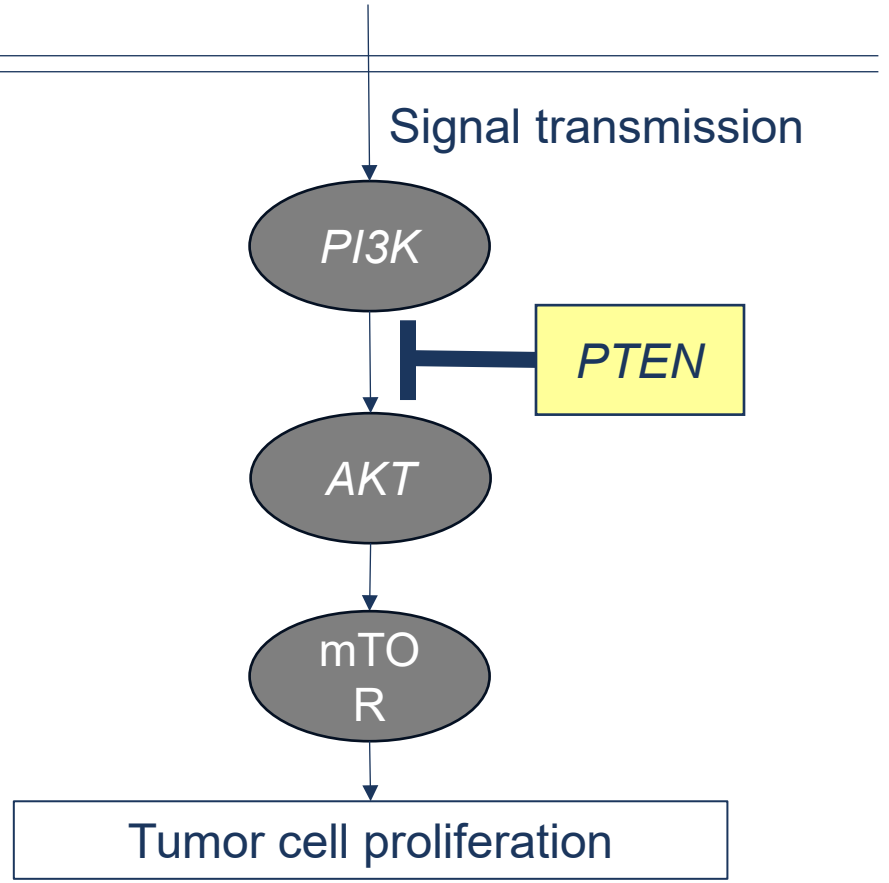
Frontline, Endocrine Resistant *PIK3CA* mutated

Inavolisib + palbociclib + fulvestrant

Alterations in *PI3K*/*AKT*/*PTEN* Pathway

- Occurs in **~40%** of patients with HR+ breast cancer
- Majority of mutations in *PIK3CA*
- *PIK3CA* mutations do NOT predict benefit from CDK4/6 inhibitors, but PFS is shorter
- Less common mutations
  - *AKT1* (2-3%)
  - *PI3K* regulatory subunit alpha (1-2%)
  - Loss-of-function mutations in *PTEN* (2-4%)



Brett JO, et al. *Breast Cancer Res*. 2021; 23:85

INAVO120 Trial: *PIK3CA* inhibitor + CDK4/6 inhibitor + SERD

- N=325, patients receiving first-line therapy in ET-resistant, *PIK3CA* mutated, HR+/HER2- mBC
  - Double-blind, phase 3
  - Only allowed patients with metastatic recurrence during/within 12 months of adjuvant ET completion
  - Strict glucose requirements at enrollment (HbA1c < 6, FPG < 126)
- Treatment*
  - Inavolisib 9 mg PO daily + palbociclib 125 mg PO daily on D1-21 + fulvestrant 500 mg IM every 28 days
  - Placebo + palbociclib + fulvestrant
- Results
  - mPFS **15** versus **7.3** months

  (HR 0.43; 95% CI 0.43-0.97, **p < 0.0001**)
  - **Overall survival positive** 34.0 months vs 27.0 months (HR, 0.67; P=0.02)
  - ORR 62.7% vs 28.0% (P<0.001).

Recent FDA Approval

- 10/10/2024
- For patients with endocrine-resistant, *PIK3CA* mutated, HR+/HER2- metastatic or locally advanced breast cancer following adjuvant endocrine therapy

Turner NC, et al. *N Engl J Med*. 2024;391:1584-1596. Jhaveri K, et al. N Engl J Med 2025;393

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Second-Line Endocrine Resistant after CDK4/6i

PIK3CA mutated:

- Alpelisib plus fulvestrant
- Capivasertib plus fulvestrant

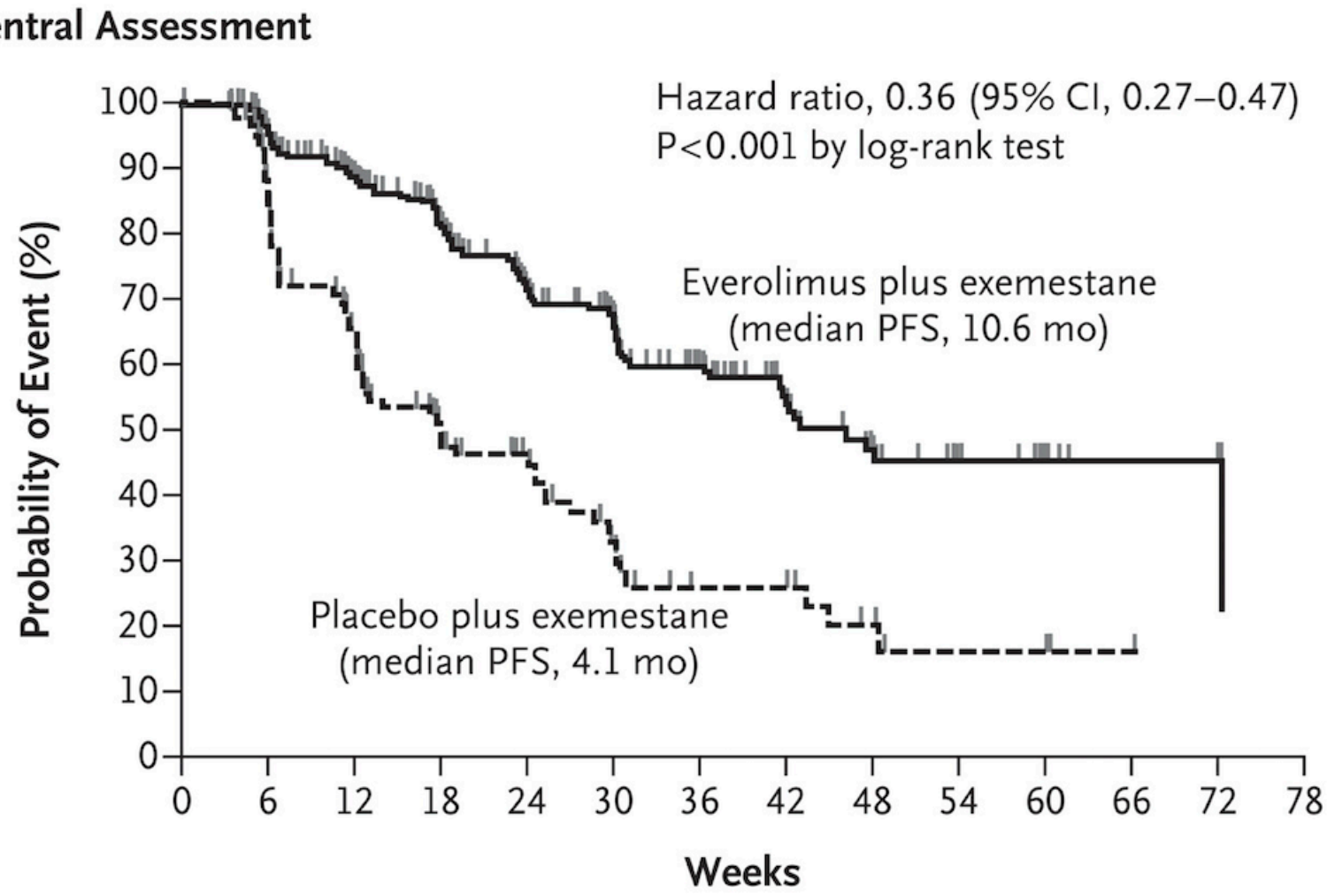
PIK3CA non-mutated (wild-type)

- Everolimus plus endocrine therapy (exemestane, fulvestrant or tamoxifen)

ESR1 mutated

- Elacestrant

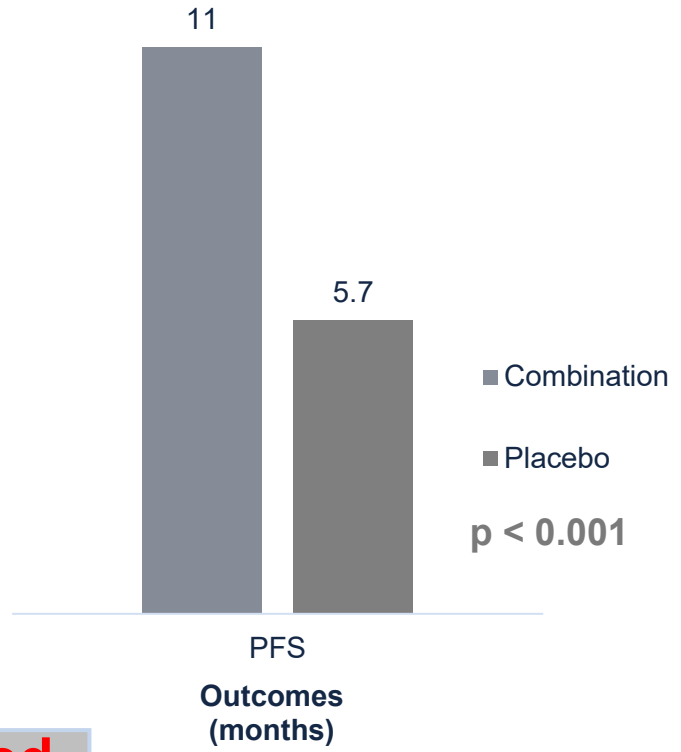
BOLERO-2: Everolimus (mTOR inhibitor) + Exemestane after progression on endocrine therapy (*PIK3CA* mut or wild type)



Baselga J et al. N Engl J Med 2012

SOLAR-1 Trial: Alpelisib (PI3K inhibitor) + SERD for *PIK3CA* mutated breast cancer

- N=572, postmenopausal women who previously received endocrine therapy with *PIK3CA*-mutated HR+/HER2- mBC
  - Double-blind, phase 3
- Treatment*
  - Alpelisib 300 mg PO daily + fulvestrant 500 mg IM every 28 days
  - Placebo + fulvestrant
- Results
  - Overall response 26.6% vs. 12.8%
  - Grade ≥ 3 AE: hyperglycemia 36.6%, rash 10%, diarrhea 6.7%
  - No overall survival benefit



Combination therapy prolonged PFS, not OS, in *PIK3CA*-mutated, HR+/HER2- mBC

André F, et al. *N Engl J Med*;2019;380:1929-40.
André F, et al. *Ann Oncol*;2021;32(2):208-17.

CAPItello-291 Trial: Capivasertib (AKT inhibitor)+ SERD for *PIK3CA*mut, *AKT*mut or PTEN loss

- N=708, patients who previously received AI ± CDK4/6 inhibitor for their HR+/HER2- mBC
  - Double-blind, phase 3
  - Stratified based on presence or absence of *AKT*-pathway alterations
  - Prior CDK4/6 inhibitor use noted in 69.1% of patients
- Treatment*
  - Capivasertib PO 400 mg BID x 4 days followed by 3 days off + fulvestrant 500 mg IM every 28 days
  - Placebo + fulvestrant

	AKT-pathway altered population		Overall population	
	Capivasertib + Fulvestrant	Placebo + Fulvestrant	Capivasertib + Fulvestrant	Placebo + Fulvestrant
mPFS – mo	7.3	3.1	7.2	3.6
HR for disease progression/ death	0.50 (0.38-0.65)		0.60 (0.51-0.71)	
P value	< 0.001		< 0.001	

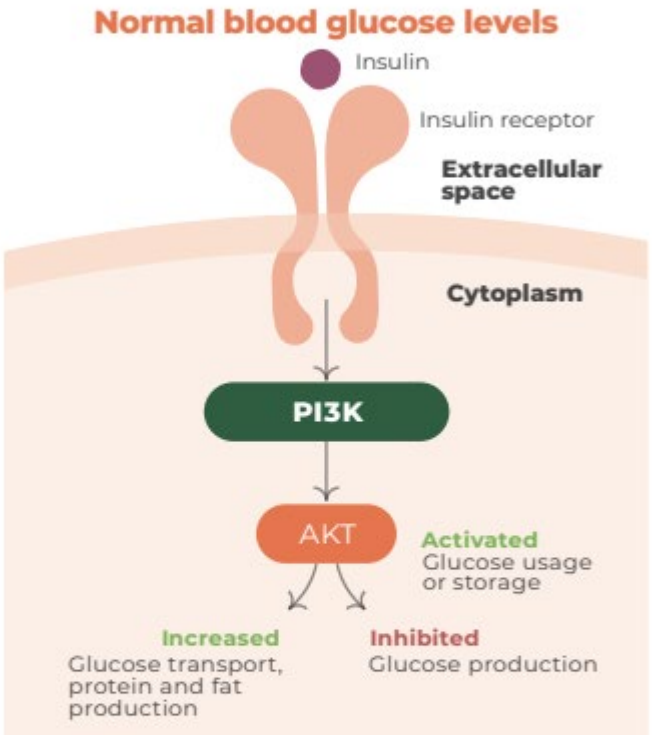
FDA Approval

- 11/16/2023
- HR+/HER2- mBC with ≥ 1 *PIK3CA/AKT1/PTEN*-alterations

Turner NC, et al. *N Engl J Med*. 2023;388:2058-2070.

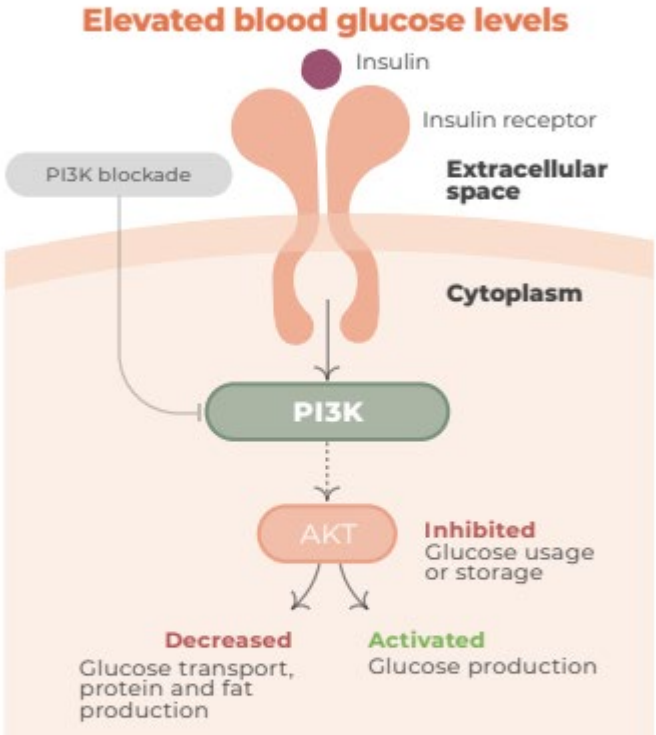
Toxicity of PI3K Pathway Inhibition

Elevated blood glucose is an expected, on-target effect of PI3K inhibition[2,4]



Insulin binds to the insulin receptor and activates the PI3K/AKT pathway, which leads to normal blood glucose levels, or **homeostasis**, due to[4,5]:

- Increased glucose transport from blood vessels, predominantly into liver, muscle, and fat cells
- Activated glucose usage for immediate energy or storage as glycogen in the liver
- Inhibited glucose production in the liver
- Increased protein and fat production



PI3K inhibition interferes with insulin–PI3K/AKT signaling, which leads to elevated blood glucose levels, or **hyperglycemia**, due to[4,6]:

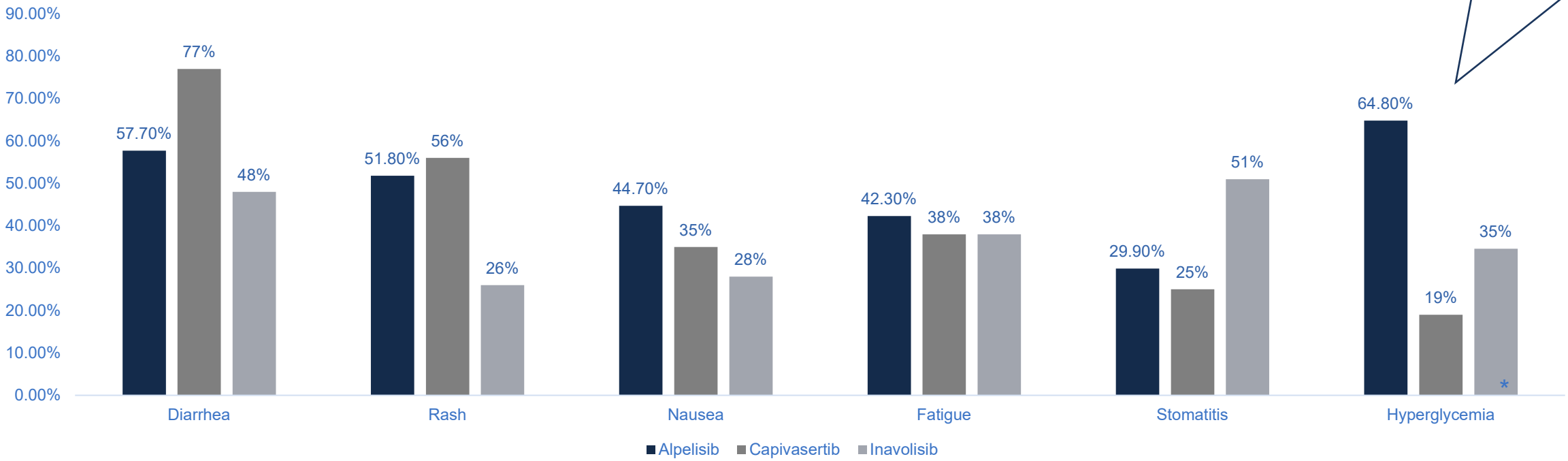
- Decreased glucose transport from blood vessels, predominantly into liver, muscle, and fat cells
- Inhibited glucose usage for immediate energy or storage as glycogen in the liver
- Activated glucose production because the liver is no longer effectively suppressed by insulin
- Decreased protein and fat production

https://www.itovebi-hcp.com/content/dam/gene/itovebi-hcp/pdfs/itovebi-hyperglycemia-management-guide.pdf

PI3K/*AKT*/mTOR Targeted Agents Toxicity Profiles

Grade ≥ 3 hyperglycemia:

- Alpelisib: 37%
- Capivasertib: 1.9%
- Inavolisib: 12.6%

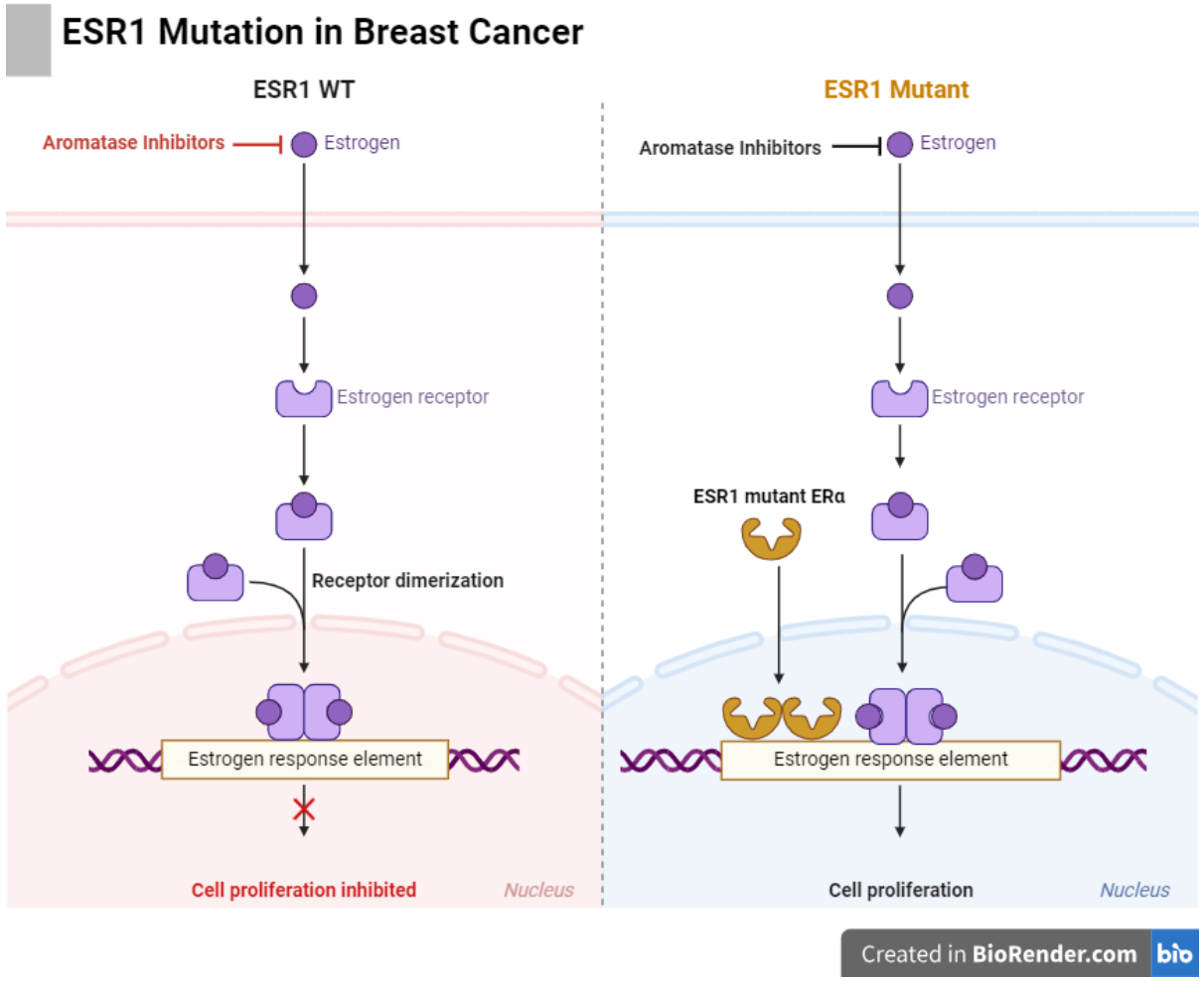


*different HgbA1c eligibility between trials

Piqray [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Co.; 2019
Truqap [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023
Itovebi [package insert]. South San Francisco, CA: Genentech USA, Inc; 2024

Estrogen-Receptor 1 (*ESR1*) Mutations

- Mechanism
  - *ESR1* is a transcription factor coding for estrogen receptor (ER) alpha protein
  - After exposure to ET, *ESR1* mutation may develop leading to constitutive activation of ER pathway
- Prevalence
  - Dependent on time of testing
  - Occurs in **40-50%** of patients who have been previously exposed to an AI
    - **< 1%** of patients that have treatment-naive BC
    - **4-5%** of patients that receive adjuvant AI
    - **50%** of patients after one year of first-line CDK4/6 inhibitor + AI
- Consequences
  - Associated with poor response to AI with shorter PFS and 1-year OS



Brett JO, et al. *Breast Cancer Res*. 2021; 23:85
Chaudhary N, et al. *NPJ Breast Cancer*. 20024;10(10:15.
Andujar JMC, et al. *Cancer Drug Resist*. 2025;8:5.
Reprinted from "ESR1 Mutation", by BioRender.com (2025). Retrieved from https://app.biorender.com/biorender-templates

EMERALD Trial: oral SERD Elacestrant for *ESR1* mutated breast cancer

- N=477, postmenopausal women and men receiving second- or subsequent-line therapy for their HR+/HER2- mBC
  - International, multicenter, randomized, open-label phase 3 trial
  - Stratified based on *ESR1* mutation status and prior fulvestrant use

- Treatment*
  - Elacestrant 345 mg PO daily
  - Standard-of-care [Fulvestrant (n=166); AI (n=73)]

- Results
  - All patients: **2.8 months** vs. 1.9 months (HR 0.70; 95% CI 0.55-0.88; p= 0.0018)
  - Patients with *ESR1* mutated cancer: **3.8 months** v. 1.9 months (HR 0.55; 95% CI 0.39-0.77; p= 0.0005)
  - Benefit greatest in those with endocrine sensitive disease (e.g. PFS of at least 12 mos on prior CDK4/6i)

Exploratory analysis mutated population showed HR 0.86; 95% CI 0.36-1.19of PFS in non-*ESR1*

FDA approved on 1/27/23 for postmenopausal men and women with HR+/HER2-, *ESR1* mutated advanced or metastatic breast cancer following disease progression on ≥ 1 ET

Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246-3256. Bardia A et al. Clin Cancer Res 2024. https://pubmed.ncbi.nlm.nih.gov/39087959/

Summary: Biomarker Driven Treatment Selection HR+, NCCN v4.2025

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection[t]**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
HR-positive, HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Inavolisib + palbociclib + fulvestrant[u]	Category 1	Useful in certain circumstances first-line therapy
HR-positive/ HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Alpelisib + fulvestrant[v]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, PCR	Capivasertib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy in select patients[w]
HR-positive/ HER2-negative[x]	*ESR1* mutation[x]	NGS, PCR	Elacestrant	Category 2A	Other recommended regimen subsequent-line therapy

Note: PARPi (olaparib or talazoparib) available for patients with BRCA1/2 mutation

Note: Everolimus + endocrine therapy available for patients without PI3K-pathway activation

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Treatment after Exhausting Endocrine Based Approaches

After exhausting endocrine therapy…. (NCCN v4.2025)

HR-Positive and HER2-Negative with Visceral Crisis† or Endocrine Refractory		
See BINV-Q (1) for Considerations for Systemic Therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b] and/or HER2 IHC 0+, 1+, or 2+/ISH negative[d]	Systemic chemotherapy[e] (category 1, preferred) BINV-Q (5), or fam-trastuzumab deruxtecan-nxki[e,f] (other recommended regimen)
	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[f] (category 1, preferred)
	HER2 IHC 0+[d]	Fam-trastuzumab deruxtecan-nxki[f] (other recommended regimen)
	Not a candidate for fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan[g] (category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
		Targeted therapy BINV-Q (6) and BINV-Q (7)
		For HER2 IHC 0, 1+, or 2+/ISH negative:[d] Datopotamab deruxtecan-dlnk[h] (other recommended regimen)
Third Line and beyond	Any	Systemic chemotherapy BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents and emerging biomarker options BINV-Q (6), BINV-Q (7), and BINV-Q (8)

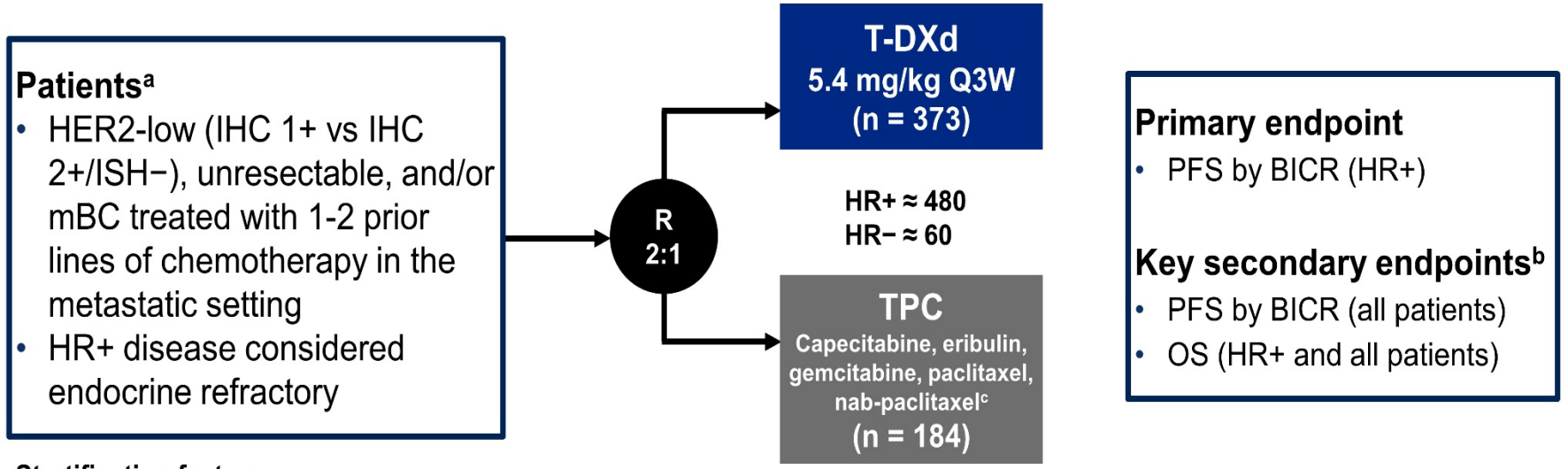
ADCs Approved for HR+ HER2- MBC

ADC Attributes	Sacituzumab govitecan (SG)	Datopotamab deruxtecan (Dato-DXd)	Trastuzumab deruxtecan
Target	TROP2	TROP2	HER2
Antibody	hRS7 IgG1k	Datopotamab	Trastuzumab
DAR	~7.6:1	~4:1	~8:1
Linker	Hydrolysable	Tetrapeptide-based	Tetrapeptide-based
Cleavable linker?	Yes	Yes	Yes
Payload	SN-38	DXd	DXd
Payload MoA	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor
Membrane permeable?	Yes	Yes	Yes

ADC, antibody-drug conjugate; DAR, drug to antibody ratio; Dato-DXd, datopotamab deruxtecan; HER2/3, human epidermal growth factor receptor 2/3; IgG, immunoglobulin; MMAE, monomethyl auristatin E; MoA, mechanism of action; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TROP, trophoblast cell surface antigen.

DESTINY-Breast04: Phase III Trial of T-DXd in HER2 low breast cancer

An open-label, multicenter study (NCT03734029)

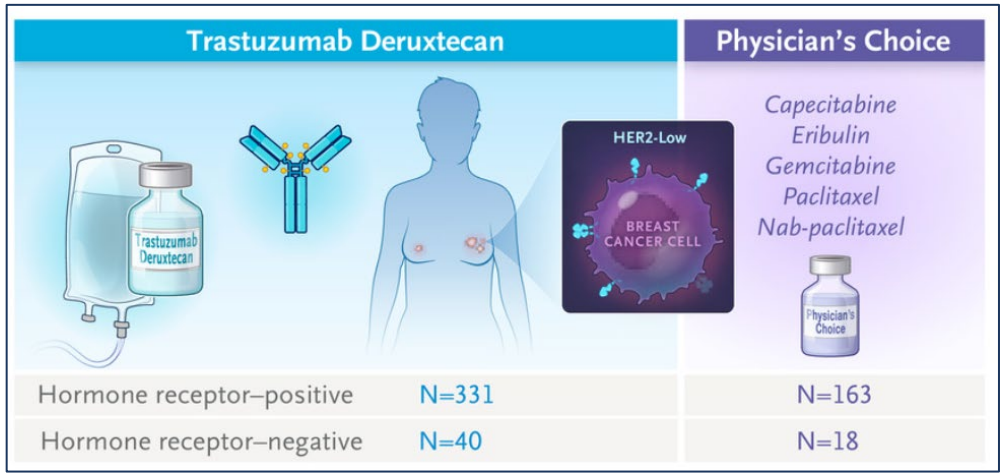


Stratification factors

- 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.

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



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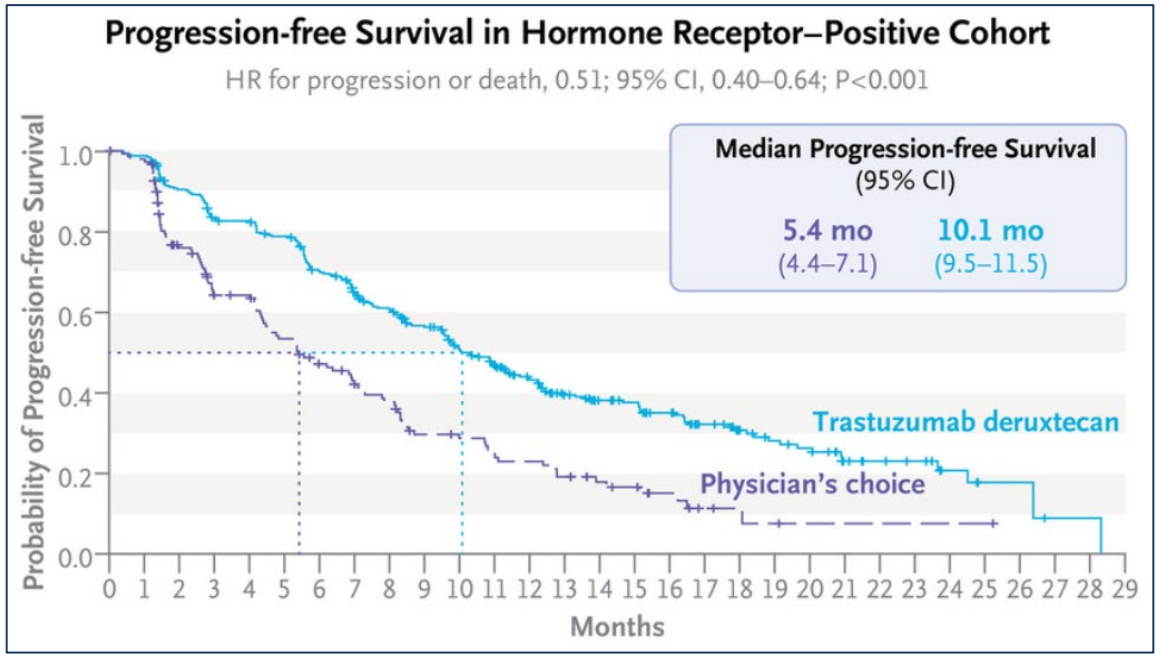
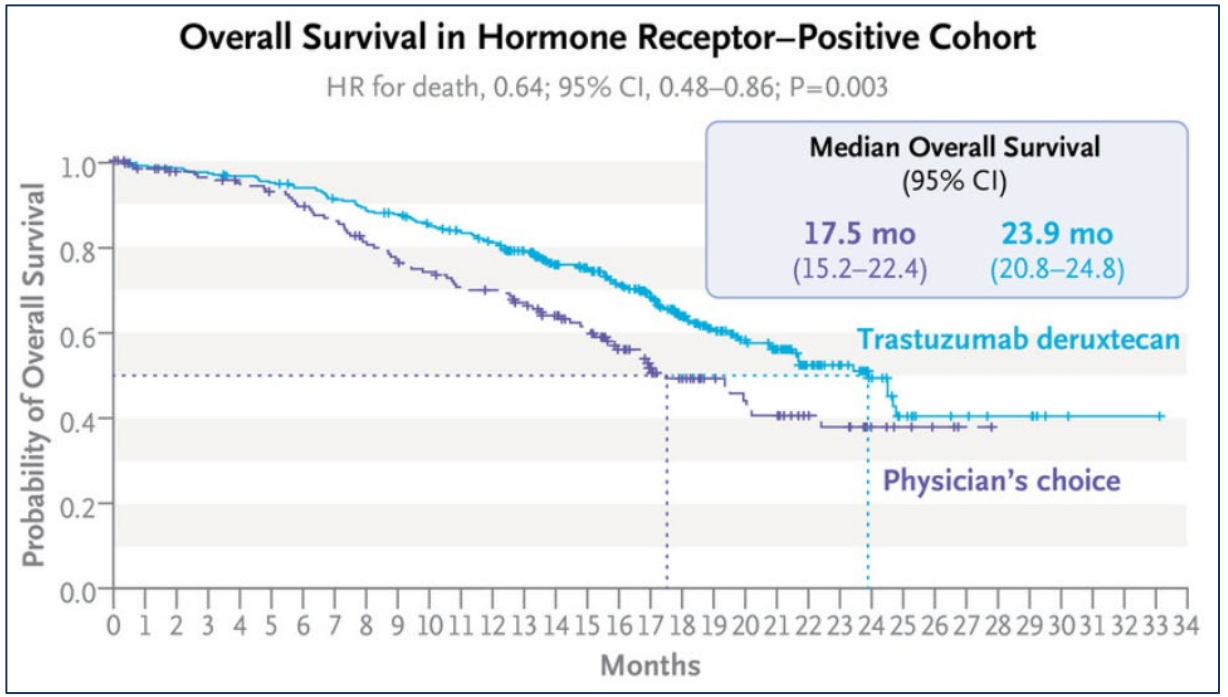
Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer





FDA Approval for HER2 low August 5, 2022
After 1 line of chemo for MBC
(HR+ or TNBC, 1+ or 2+/FISH negative)

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

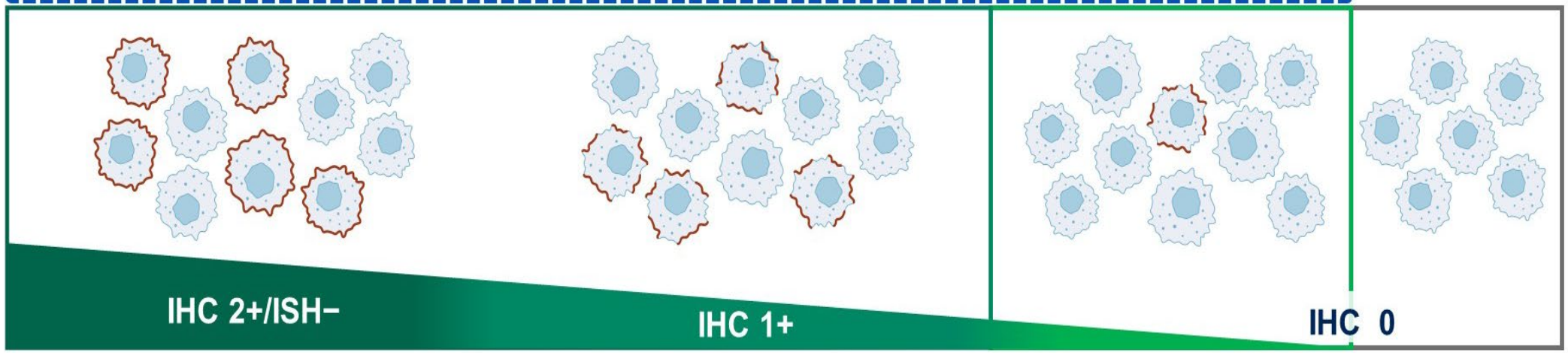
Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC

HER2-low ~60–65%[2,3]

HER2-ultralow ~20–25%[2–4]



IHC 2+/ISH−	IHC 1+	IHC 0	
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	**Faint, incomplete membrane staining in ≤10% tumor cells**	Absent / no observable membrane staining

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

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

DESTINY-Breast06: HR+ HER2 Low or Ultralow

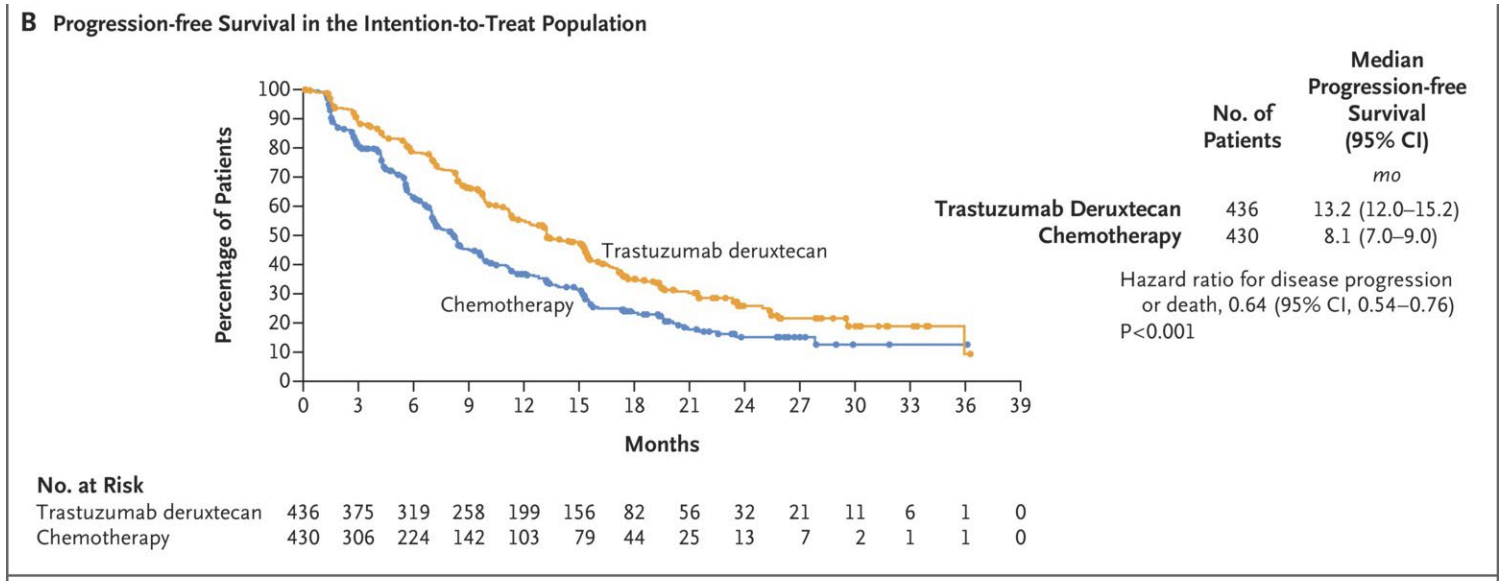
PATIENT POPULATION

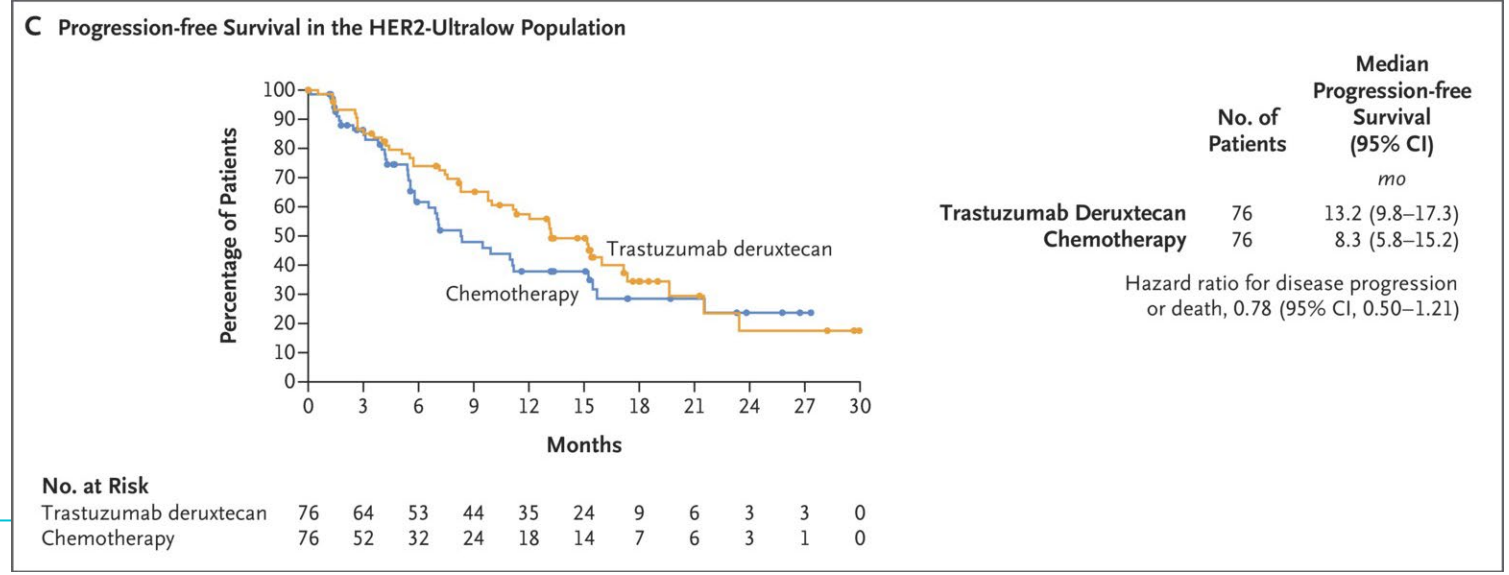
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

- Overall survival not mature, thus far not significant
- FDA Approval for HER2 ultralow (IHC 0 with membrane staining) January 27, 2025



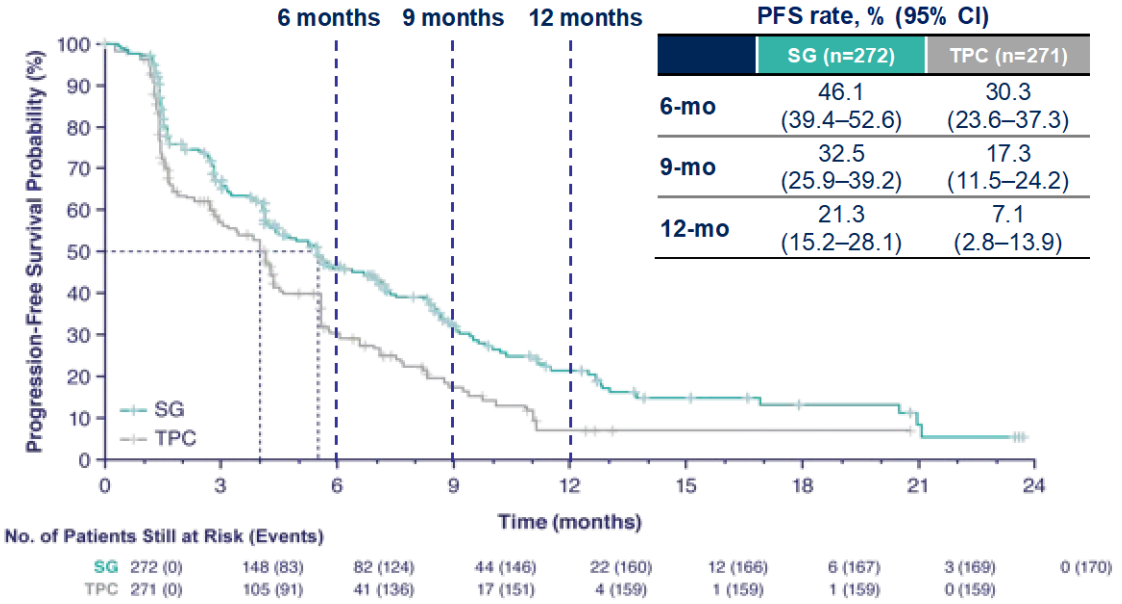


Bardia A et al. *N Engl J Med*. 2024;391(22):2110-2122.

TROPiCS-02: TROP2 ADC (sacituzumab govitecan) vs TPC
≥1 endocrine therapy, ≥1 CDK4/6 inhibitor, a taxane, and 2-4 chemo for MBC

PFS

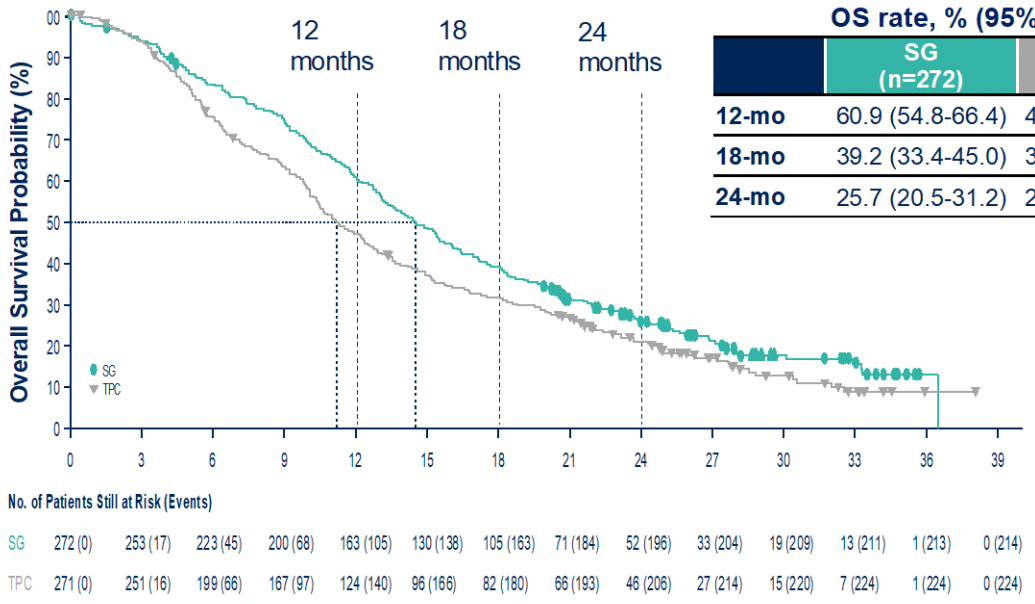
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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

OS

	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	*P*=0.0133	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

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

Bardia et al. N Engl J Med 2021;384. Rugo et al. Lancet 2023;402.

TROPiCS-02
Sacituzumab govitecan

Safety summary

n (%)		SG (n=268)		TPC (n=249)	
AE Grade ≥3		199 (74)		149 (60)	
AEs → discontinuation		17 (6)		11 (4)	
AEs → dose delay		178 (66)		109 (44)	
AEs → dose reductions		91 (34)		82 (33)	
SAEs		74 (28)		48 (19)	
AEs → death[a]		6 (2)		0	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic	**Neutropenia**	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia	17 (6)	1 (<1)	41 (16)	9 (4)
GI	**Diarrhea**	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

[a]Of 6 AEs leading to death, 1 (septic shock due to neutropenic colitis) was considered treatment related by investigator

Patients will lose ALL their hair (underreported in clinical trials)

Bardia et al. N Engl J Med 2021;384. Rugo et al. Lancet 2023;402.

TROPION-Breast01: TROP2 ADC Datopotamab deruxtecan vs chemo

Key eligibility
- HR+/HER2−[a] breast cancer
- Previously treated with 1–2 lines of chemo (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0/1

R 1:1

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

TPC[b]
(n=367)

Continue until PD, unacceptable toxicity / other discontinuation criteria

Dual primary endpoints[c]:
- PFS by BICR
- OS

Key secondary endpoint:
- ORR
- PFS (investigator assessed)
- Safety

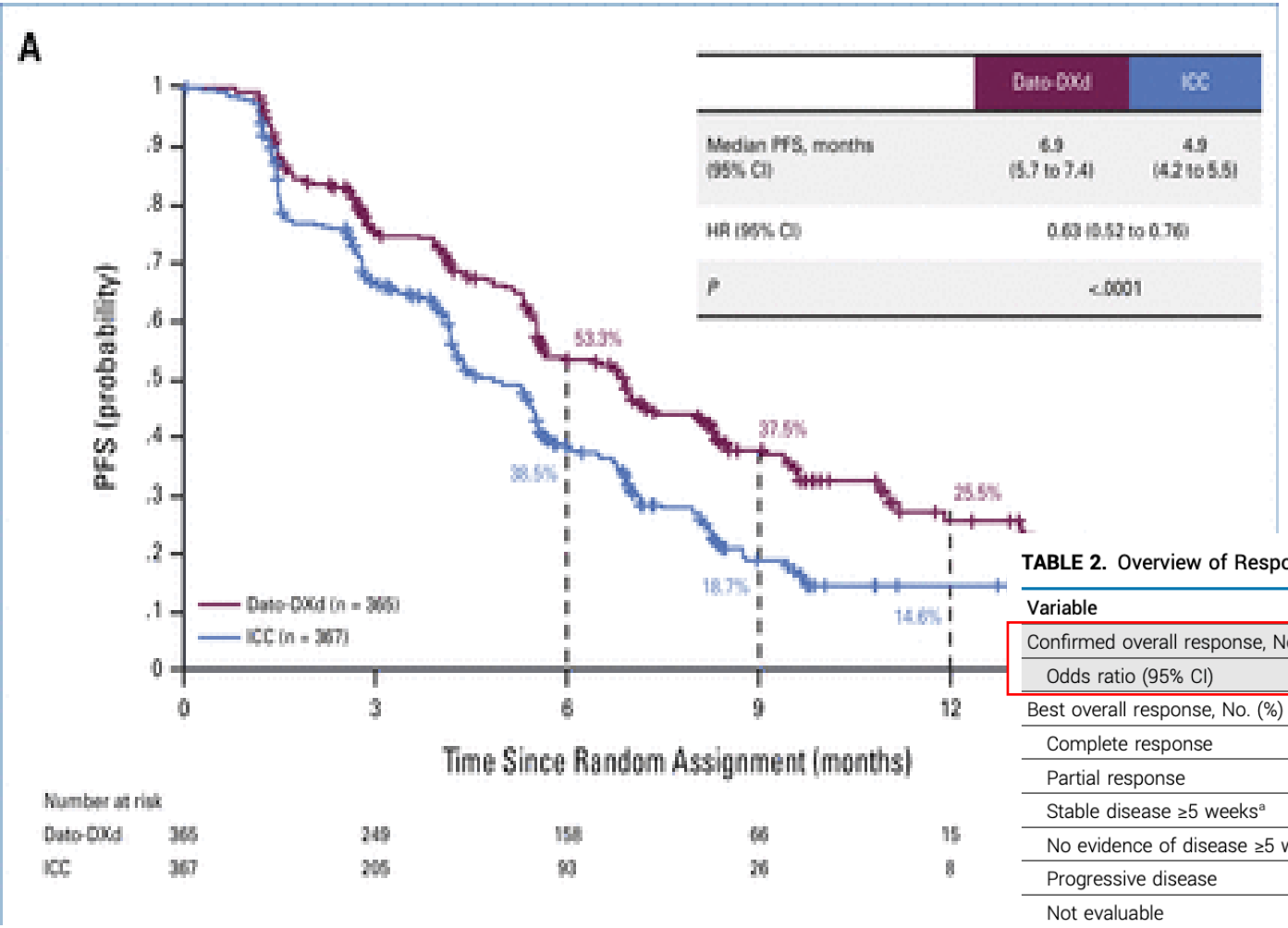
Stratification factors
- Lines of chemo in unresectable/ metastatic setting (1 vs 2)
- Geographical location (US/Canada/ Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

- **At data cutoff (July 17, 2023), patients remaining on treatment:**
  - **Data-DXd, n=93**
  - **TPC, n=39**
- **Median follow-up: 10.8 months**
- **Median one line of prior therapy**

[a]IHC 0/1+/2+; ISH−; [b]Investigator's choice of chemotherapy; [c]By BICR per RECIST v1.1.
Dato-DXd, datopotamab deruxtecan; TPC, treatment of physician's choice.

Bardia et al. SABCS 2023. Abstract GS02-01.

TROPION-Breast01 PFS and ORR



Fred Hutchinson Cancer Center

Bardia et al. J Clin Oncol. 2024;43

Press Release: AstraZeneca Sept 23, 2024

Survival results for datopotamab deruxtecan in TROPION-Breast01 did not achieve statistical significance versus chemotherapy

TABLE 2. Overview of Response by BICR (intention-to-treat population)

Variable	Dato-DXd (n = 365)	ICC (n = 367)
Confirmed overall response, No. (%)	133 (36.4)	84 (22.9)
Odds ratio (95% CI)	1.95 (1.41 to 2.71)	
Best overall response, No. (%)		
Complete response	2 (0.5)	0
Partial response	131 (35.9)	84 (22.9)
Stable disease ≥5 weeks[a]	168 (46)	176 (48)
No evidence of disease ≥5 weeks	1 (0.3)	0
Progressive disease	58 (15.9)	76 (20.7)
Not evaluable	5 (1.4)	31 (8.4)
Incomplete postbaseline assessments	5 (1.4)	28 (7.9)
Stable disease <5 weeks	0	2 (0.5)
Death	0	1 (0.3)[c]
Disease control rate at 12 weeks, %[b]	275 (75.3)	234 (63.8)
Median duration of response, months (95% CI)	6.7 (5.6 to 9.8)	5.7 (4.9 to 6.8)
Median time to response, months (IQR)	2.7 (1.4-3.9)	2.6 (1.4-2.9)

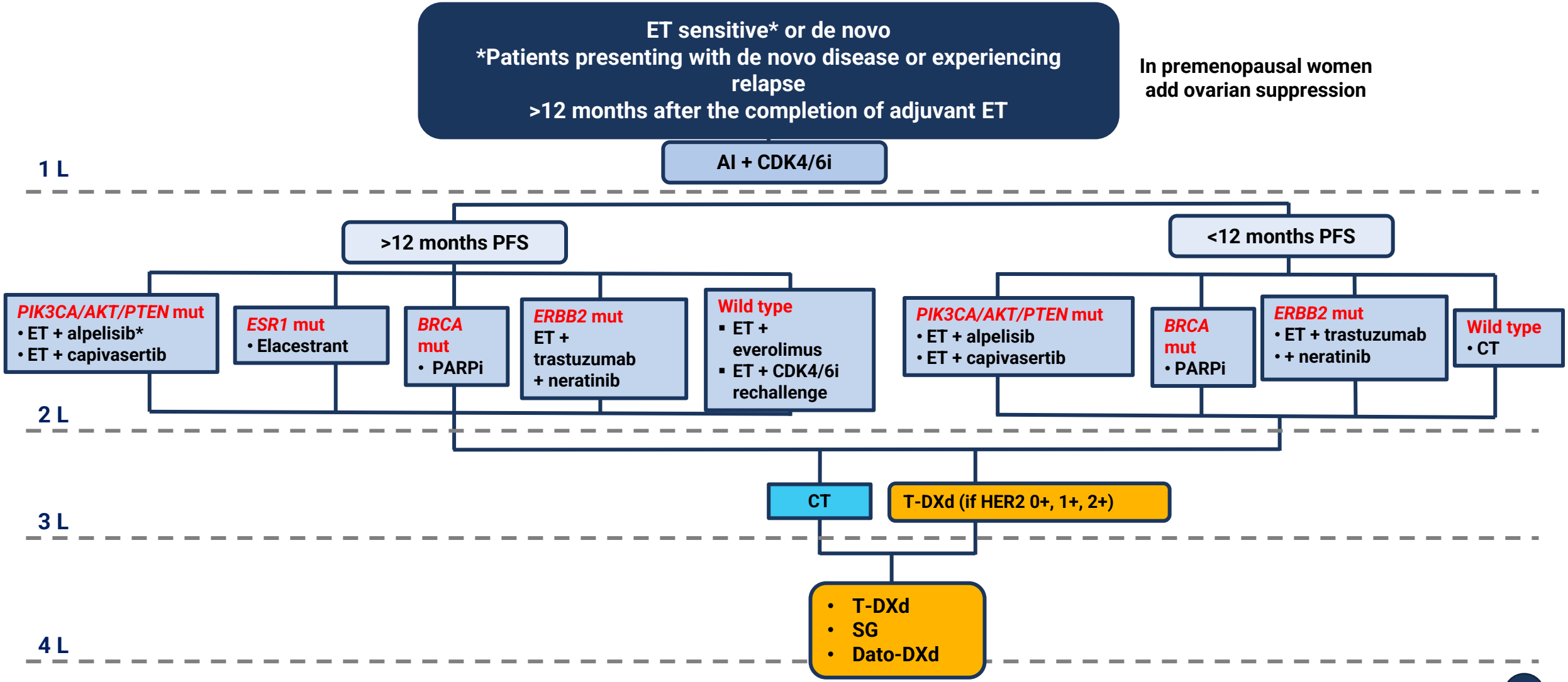
Summary: First- and Second-Line Treatment Options

HR+/HER2- Advanced Breast Cancer

Line of Therapy	Mutation Status	Treatment Option
1L	Any	ET+ CDK4/6i
1L	*PIK3CA*^{mt}; recurrence ≤12 months from adjuvant endocrine therapy; acceptable glucose at baseline	ET+ CDK4/6i + inavolisib
2L	*PIK3CA*^{mt}	Alpelisib + fulvestrant
2L	*PIK3CA*^{mt}/*AKT1*^{mt}/PTEN^{loss}	Capivasertib + fulvestrant
2L	*ESR1*^{mt}	Elacestrant
2L	g*BRCA1/2*^{mt}	PARPi
2L	None/Not Known	Everolimus + ET CDK4/6i (switch) + ET Single agent endocrine therapy ADC, Chemotherapy

1L, first line; 2L, second line; ESR1, estrogen receptor 1; gBRCA, breast cancer gene; PARPi, poly(ADP-ribose) polymerase inhibitors; PIK3CA, gene which encodes the p110 alpha catalytic subunit of PI3K; PTEN, phosphatase and tensin homolog.

Optimizing Treatment: ET Sensitive or de novo HR+/HER2– mBC

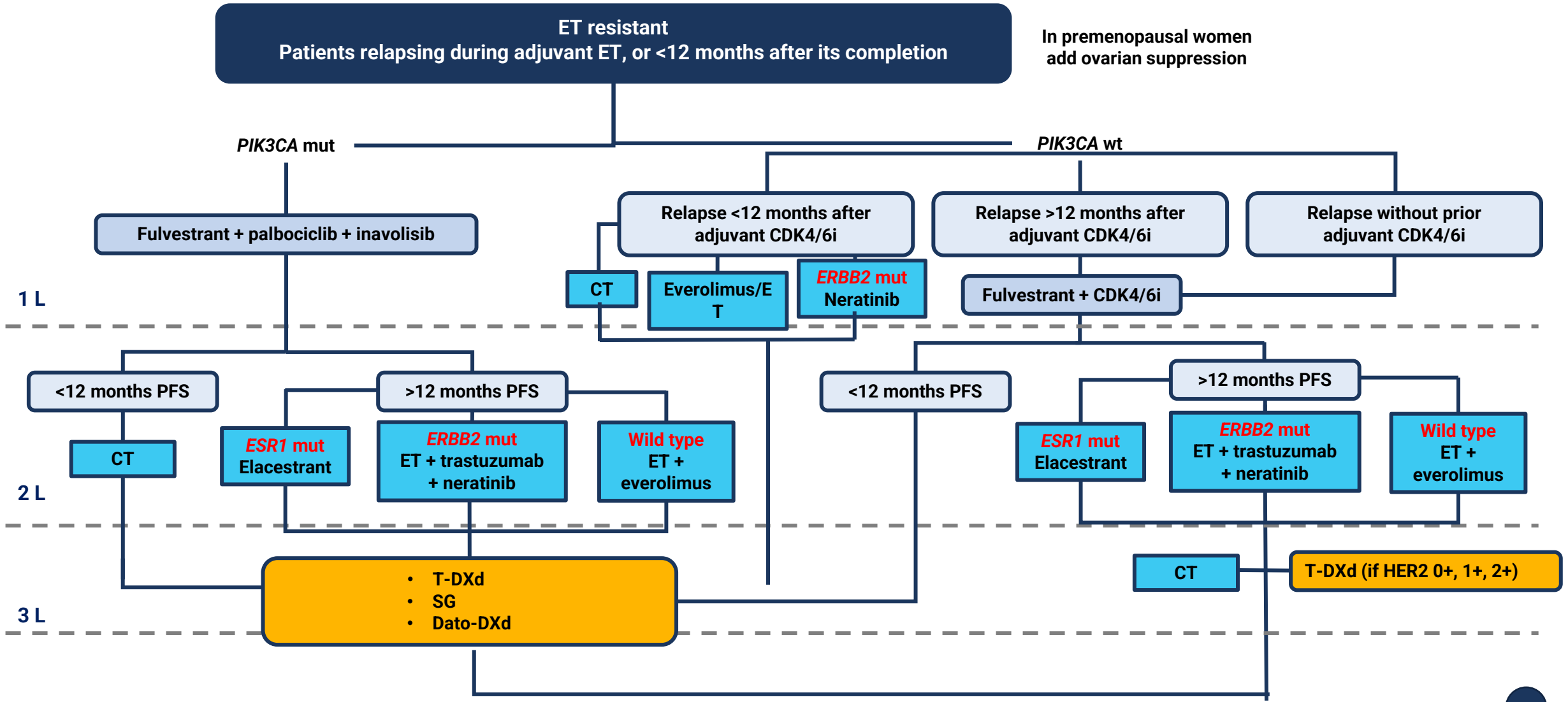


*Consider this option only for patients with mutatations in PIK3CA.

AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase inhibitors; CT = chemotherapy; ERS1 mut = estrogen receptor 1 mutation; ET = endocrine therapy; HR+ = hormone receptor-positive; HER2– = human epidermal growth factor receptor 2-negative; PARPi = poly [ADP-ribose] polymerase) inhibitor; PD = progressive disease; SG = sacituzumab govitecan; T-DXd = trastuzumab deruxtecan.

Image from Cejalvo Andújar JM, et al. *Cancer Drug Resist*. 2025;8:5.

Optimizing Treatment: ET Resistant HR+/HER2– mBC



Fred Hutchinson Cancer Center

*Expert consensus. ** Consider anthracyclines or taxanes if not previously used.

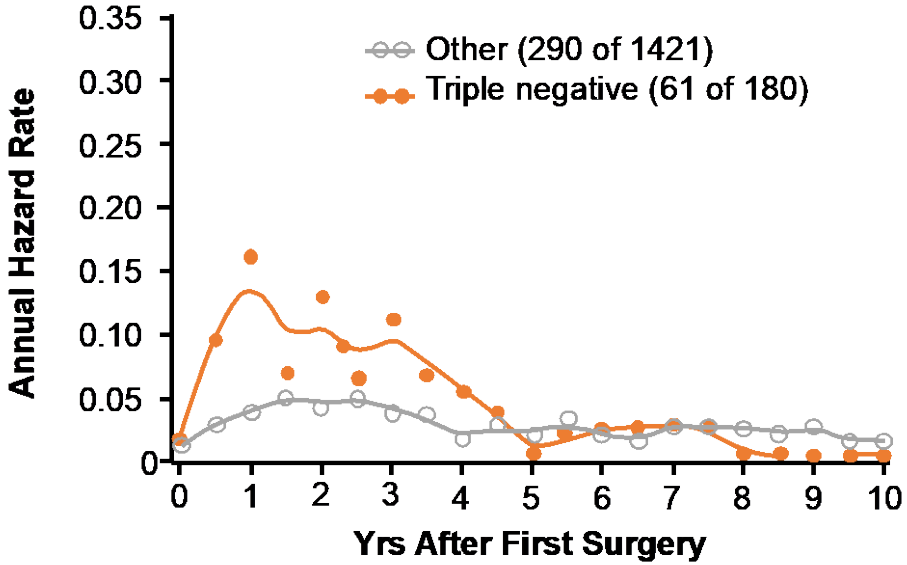
AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase inhibitors; ERS1 mut = estrogen receptor 1 mutation; ET = endocrine therapy; HR+ = hormone receptor-positive; HER2– = human epidermal growth factor receptor 2-negative; PD = progressive disease; SG = sacituzumab govitecan; T-DXd = trastuzumab deruxtecan; wt = wild type.

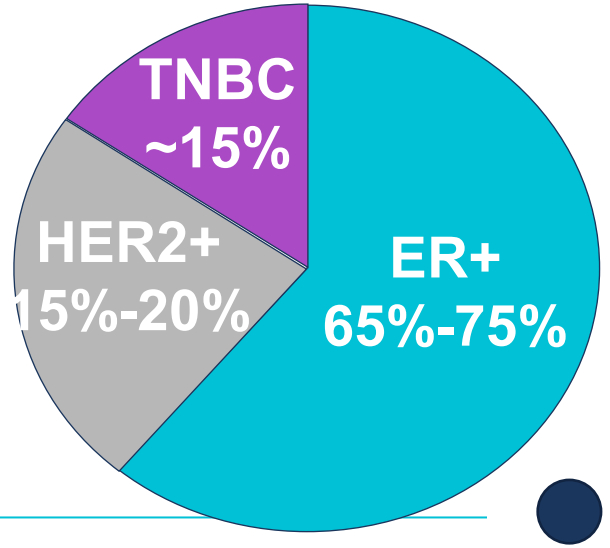
Image from Cejalvo Andújar JM, et al. *Cancer Drug Resist*. 2025;8:5.

4. Triple Negative Metastatic Breast Cancer

Triple Negative Breast Cancer

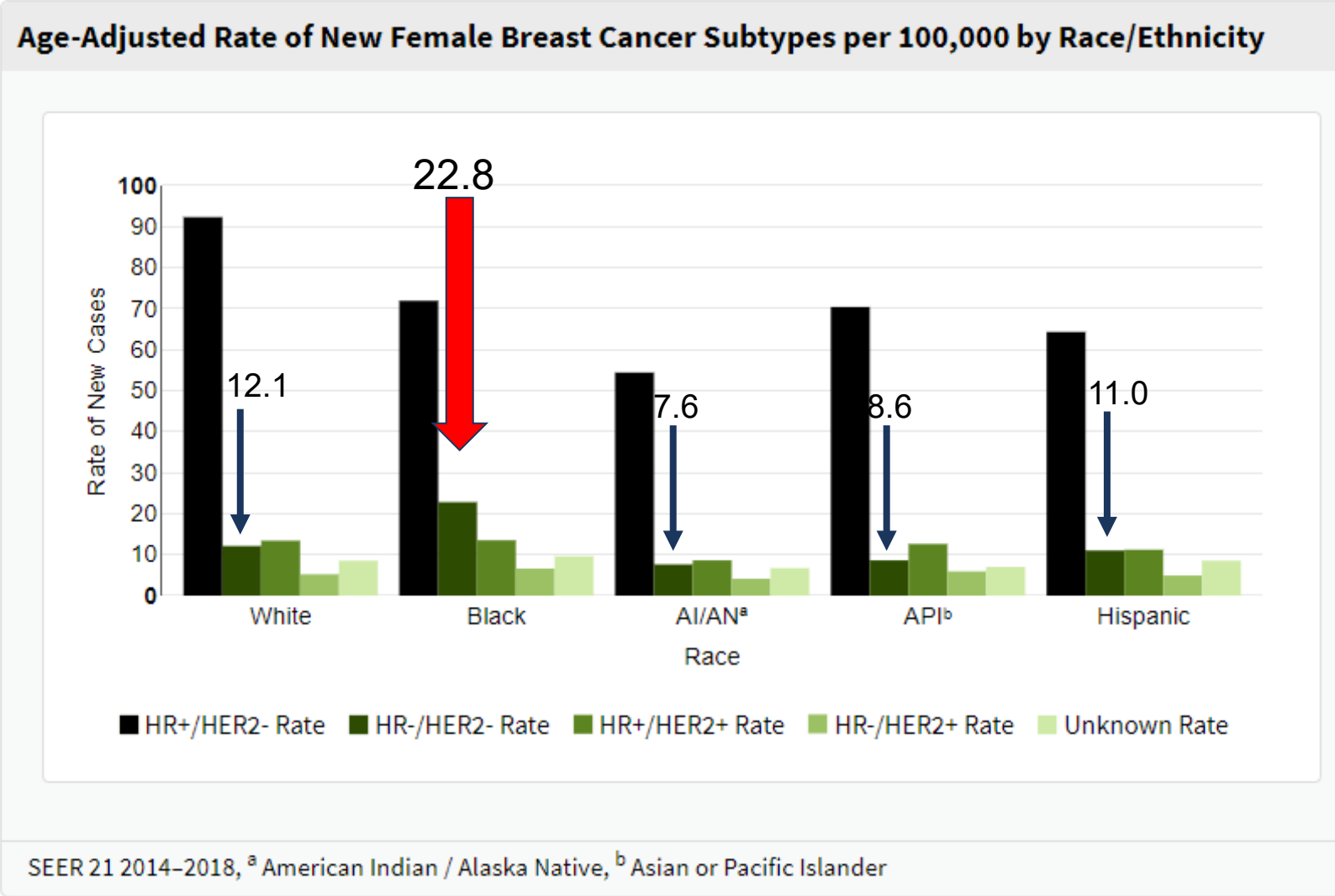
- 10-15% of all breast cancer, defined by what it is not
- Heterogeneous disease
  - Highly proliferative, usually chemotherapy responsive
  - Rapid development of resistance
- High risk of early recurrence, esp first 5 years
  - Visceral dominant disease, early/frequent brain metastases
  - Short median survival (<2yrs) after diagnosis of metastases
- Generally affects younger women; Black women have a higher proportion of TNBC than other races
- Rare indolent subtypes, generally in older women
- P53 mutations common; may be associated with *BRCA1* mutations and/or *BRCA* pathway dysfunction





Lin NU, et al. Cancer. 2008;113:2638-2645. Liedtke C, et al. J Clin Oncol. 2008;26:1275-1281. Dent R, et al. Clin Cancer Res. 2007;13:4429-4434. Ahn SG et al. *J Breast Cancer*. 2016;19(3):223-30.

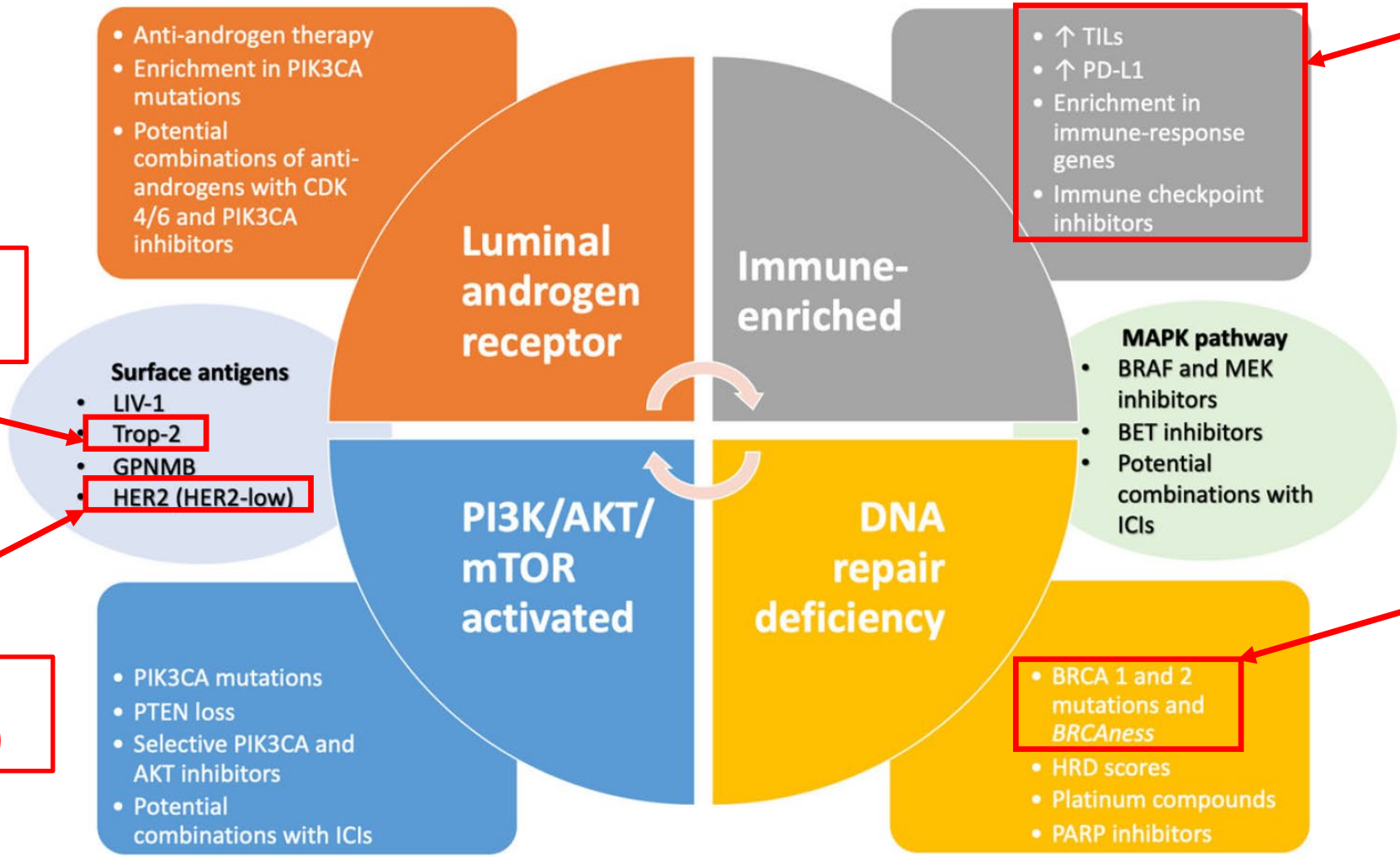
Black Women Have the Highest Rate of TNBC



- In a population-based cohort study of 23,213 patients with TNBC, African American women compared to white women[2]
  - Had lower odds of receiving surgery (OR, 0.69) or chemotherapy (OR, 0.89)
  - Breast cancer mortality was higher (HR, 1.28)
- NH Black women have a 12% higher 5-year mortality than NH White women, even when age and clinical factors are adjusted[3]

Howlader N et al. *Cancer Epidemiol Biomarkers Prev*. 2018;27(6):619-626. 2. Cho B et al. *JAMA Oncol*. 2021;7(7):1016-1023.
3. NIH. SEER Database. Cancer Stat Facts: Female Breast Cancer Subtypes. 2024.

Biomarker-Driven Therapeutic Approaches



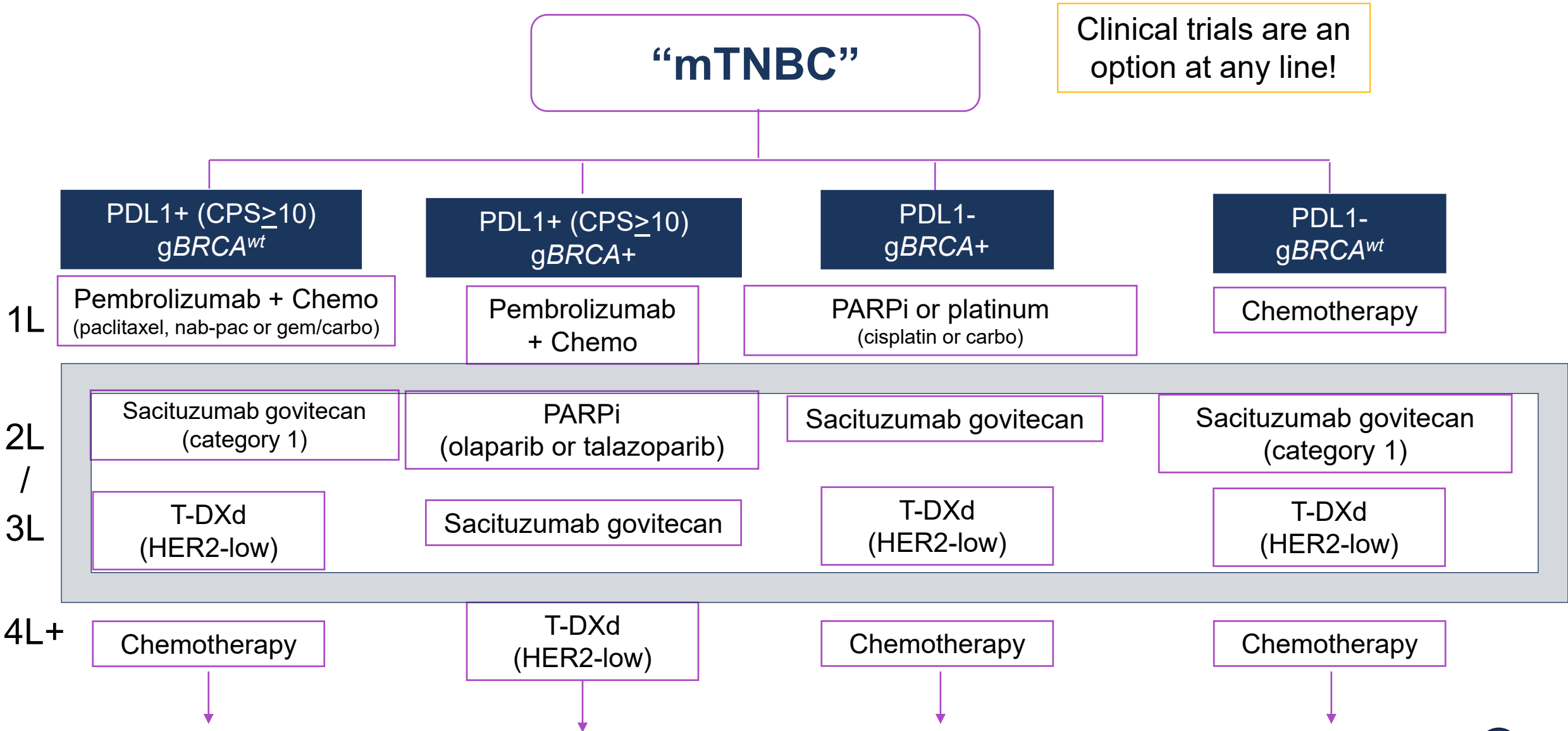
pembrolizumab

Sacituzumab govitecan

Trastuzumab deruxtecan (T-DXd)

Olaparib
Talazoparib

Marra A, et al. NPJ Breast Cancer. 2020;6:54.

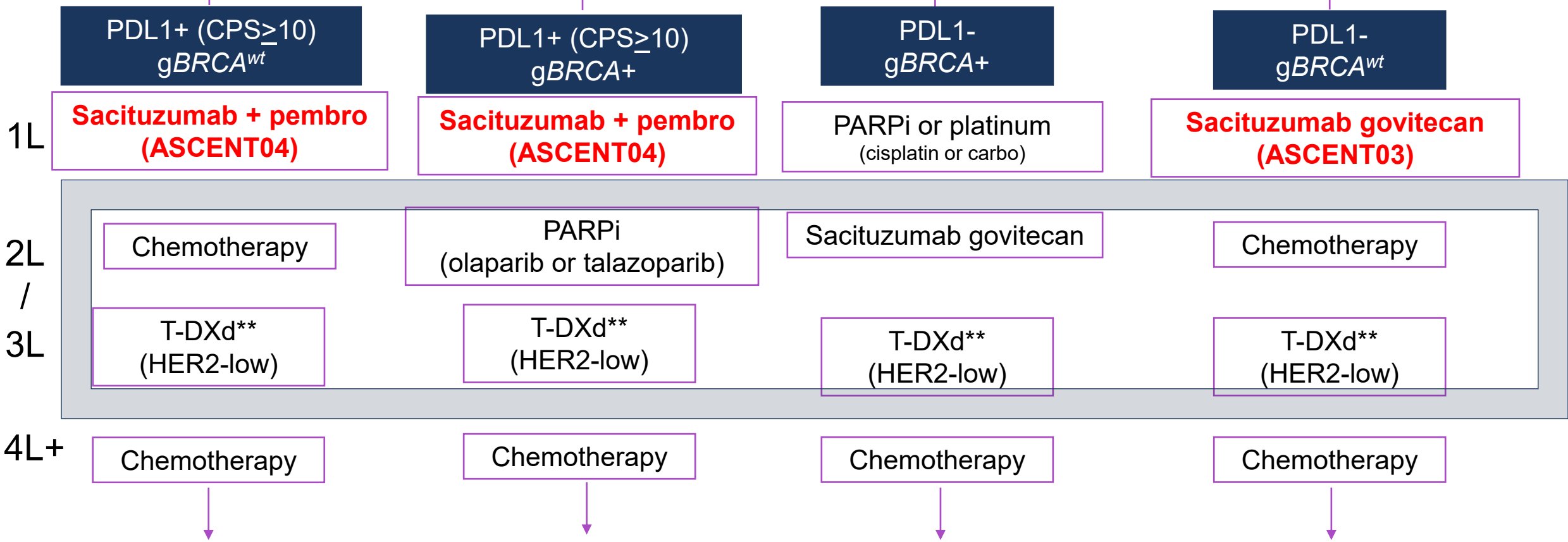


- Pembrolizumab 2L+ for solid tumors with **TMB-H (>10mut/Mb) or MSI-high**
- ***NTRK* fusion**: Larotrectinib or entrectinib for metastatic solid tumor

Adapted from NCCN v4.2025 & ESMO Guidelines.

mTNBC
POSSIBLE NEAR FUTURE

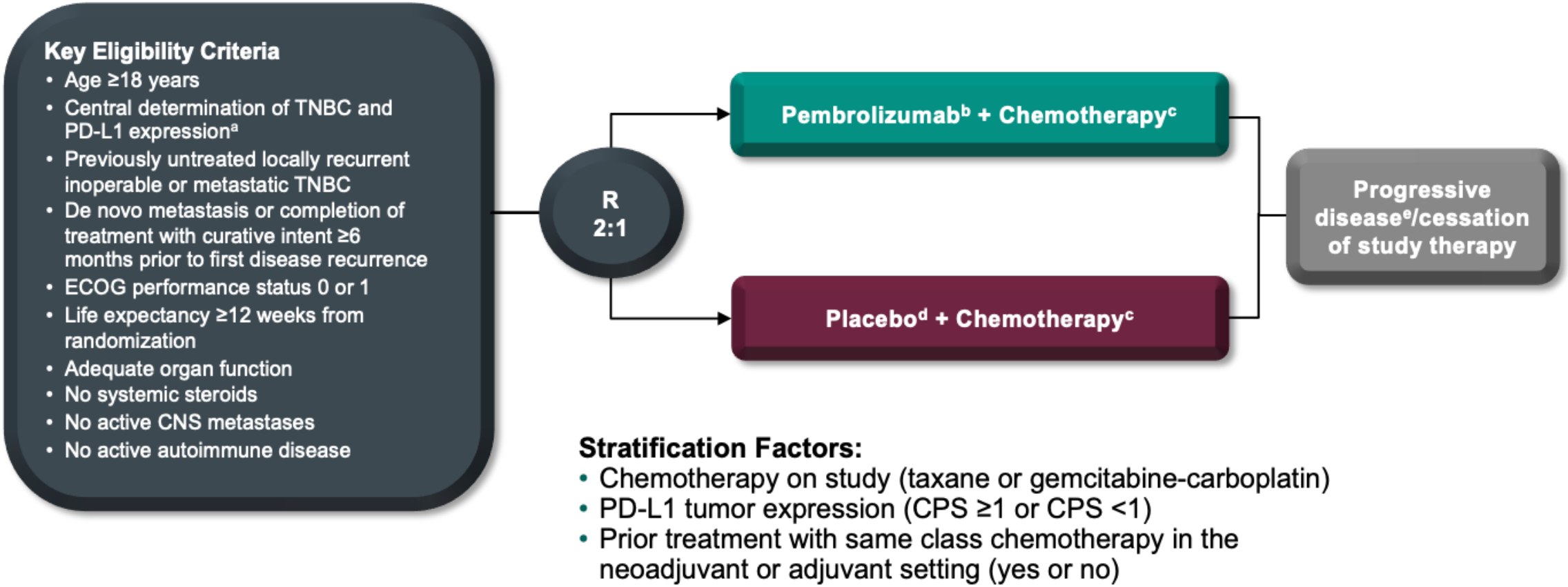
Clinical trials are an option at any line!



- **unclear benefit of using sequential ADCs (SG → T-DXd)
- Pembrolizumab 2L+ for solid tumors with **TMB-H (>10mut/Mb) or MSI-high**
- ***NTRK* fusion**: Larotrectinib or entrectinib for metastatic solid tumor

Adapted from NCCN v4.2025 & ESMO Guidelines.

KEYNOTE-355 Study Design (NCT02819518)

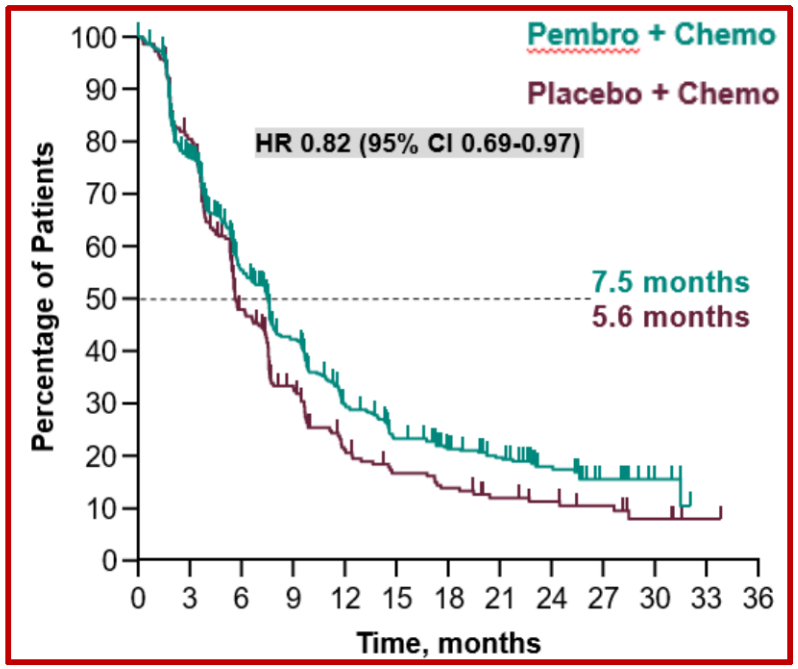


[a]Based on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumour sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). [b]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W). [c]Chemotherapy dosing regimens 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. [d]Normal saline. [e]Treatment may be continued until confirmation of progressive disease.

Cortes J, et al. *Lancet.* 2020;396:1817-1828.

KEYNOTE-355: Primary Outcome (PFS)

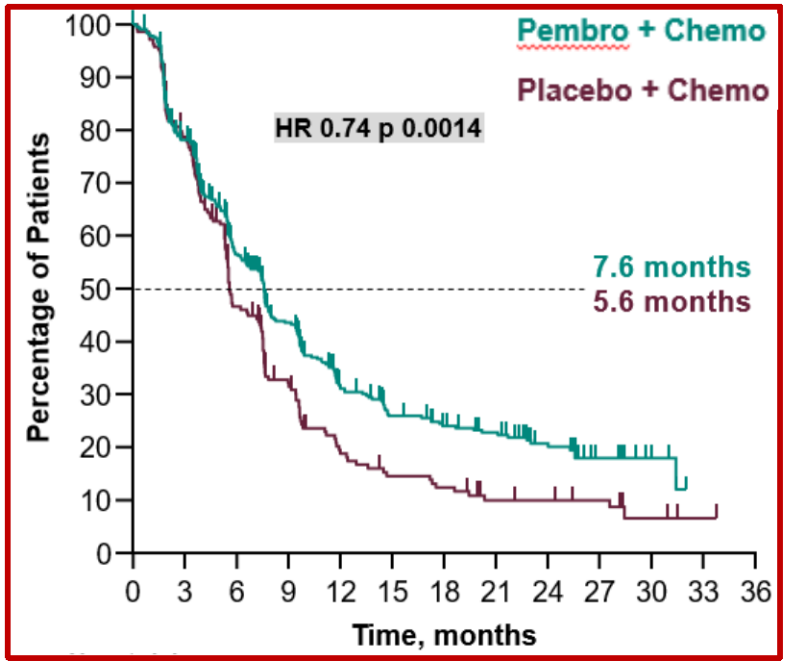
ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy.

PD-L1 CPS ≥1

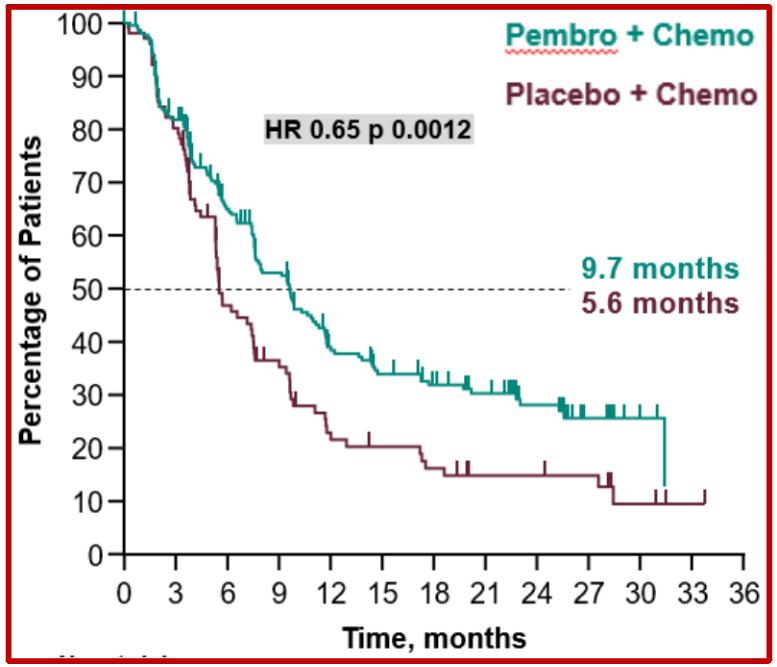
75% of patients



Prespecified *P* value boundary of 0.00111 **not** met.

PD-L1 CPS ≥10

38% of patients

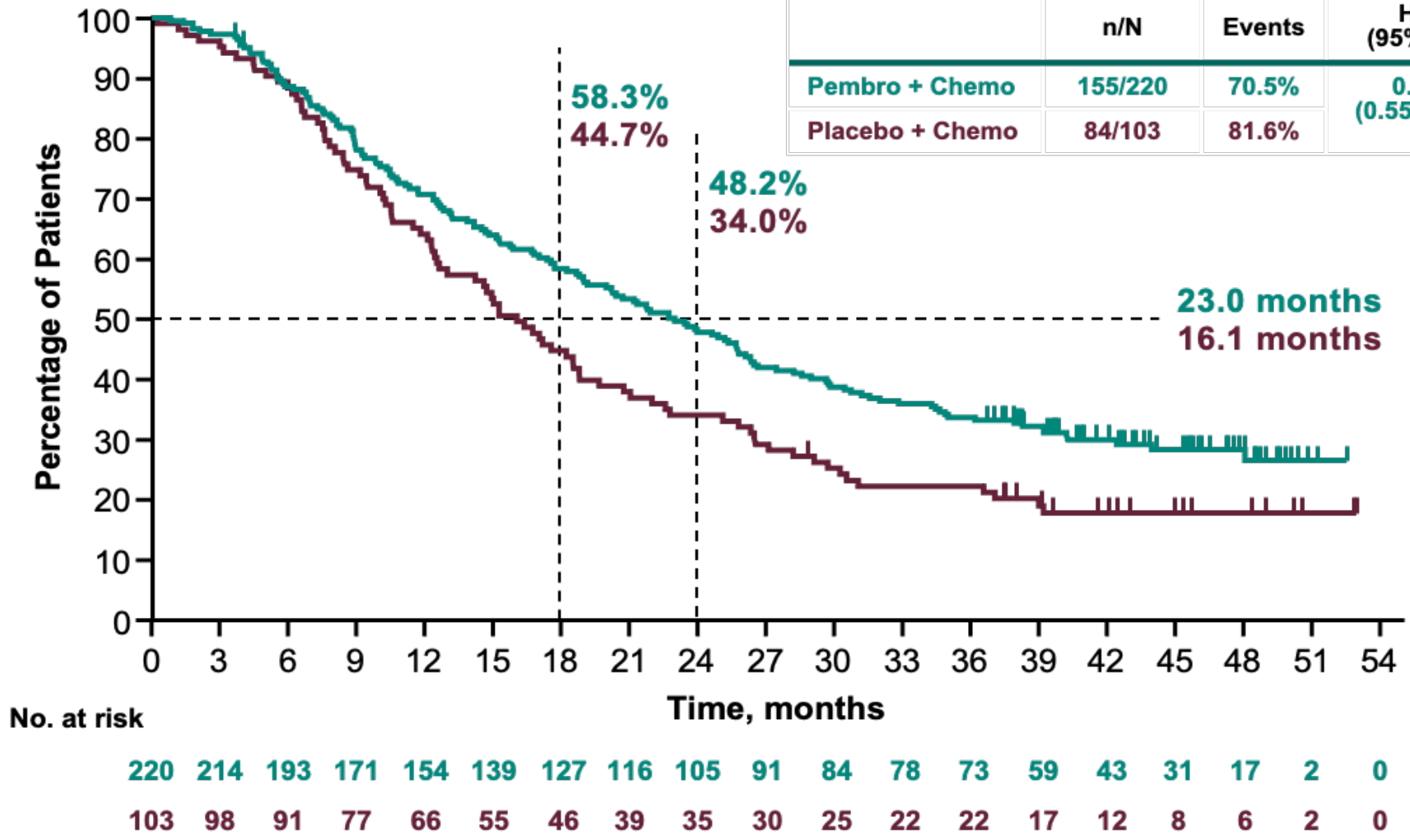


Prespecified *P* value boundary of 0.00411 met.

Cortes J, et al. ASCO 2020. Abstract 1000.

KN-355: Overall Survival in PD-L1+ Patients CPS ≥10

	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%		



[a]Prespecified Fred Hutchinson boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

Rugo HS, et al. ESMO 2021. Abstract LBA16.

Combined Positive Score (CPS) for PD-L1

Number of positive immune cells *(lymphocytes and macrophages)* and tumor cells within tumor nests and adjacent supporting stroma/total number of viable tumor cells*100

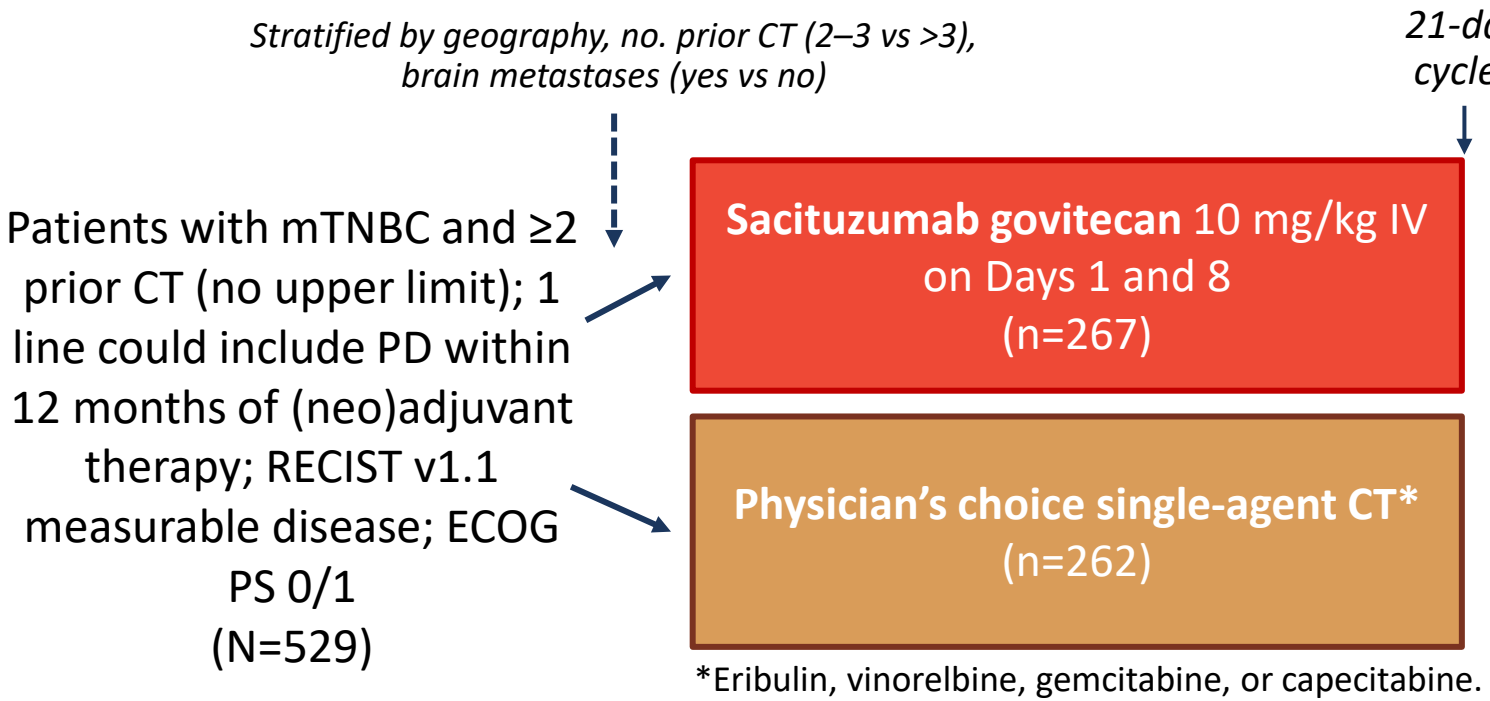
	CPS
Calculation	$\frac{\text{\# PD−L1-staining cells (tumor, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$
Assay	PD-L1 IHC **22C3** pharmDx[1]
Developed for use with	**Pembrolizumab**
Clinically relevant cut-off in TNBC	**CPS ≥10**

- PD-L1 results may differ based on site sampled[2,3]
  - Breast, lymph node, skin, lung higher likelihood PD-L1+
  - Liver lower likelihood
- PD-L1 results may differ based on timing of sampling[2,3]
  - Sample from primary diagnosis higher likelihood to be PD-L1+ than metastatic site

1. PD-L1 IHC 22C3 pharmDx Interpretation Manual – TNBC. Agilent Technologies, Inc. Nov 2020.
2. Rugo HS, et al. ESMO 2019. Abstract LBA20.
3. 3. Emens LA, et al. JNCI 2021

ASCENT: Sacituzumab Govitecan vs Single-agent CT in Metastatic TNBC after ≥2 Previous CT Regimens

- Randomized, open-label phase III trial



*Eribulin, vinorelbine, gemcitabine, or capecitabine.

- Primary endpoint: PFS by IRC in patients without brain metastases
- Secondary endpoints: PFS (full population), OS, ORR, DoR, TTR, safety

- Trial halted early based on efficacy per unanimous independent DSMC recommendation

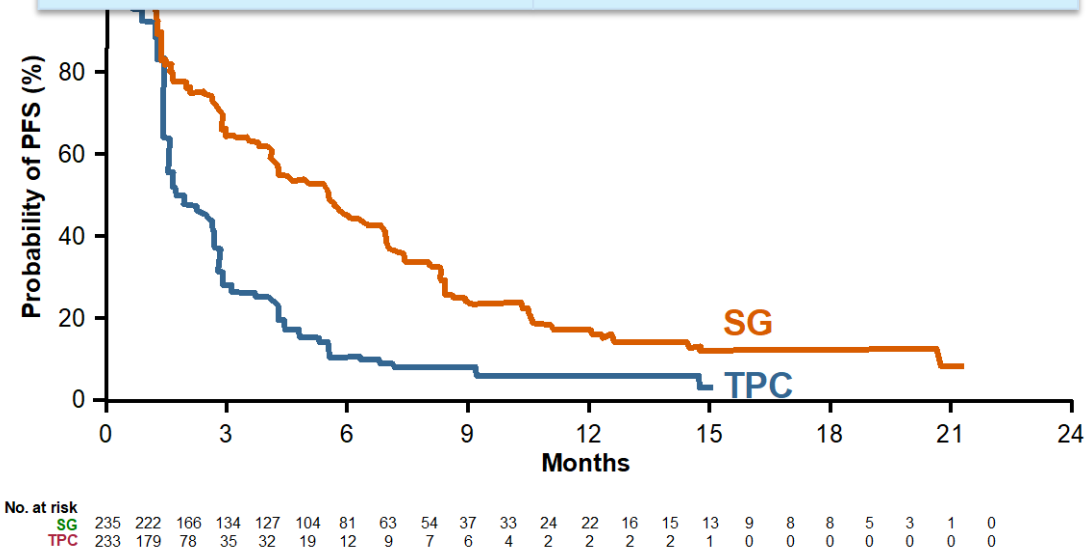
CT, chemotherapy; DoR, duration of response; DSMC, data and safety monitoring committee; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; mTNBC, metastatic triple negative breast cancer; PD, progressive disease; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

Bardia A, et al. *N Engl J Med*. 2021.

Phase 3 ASCENT: Efficacy

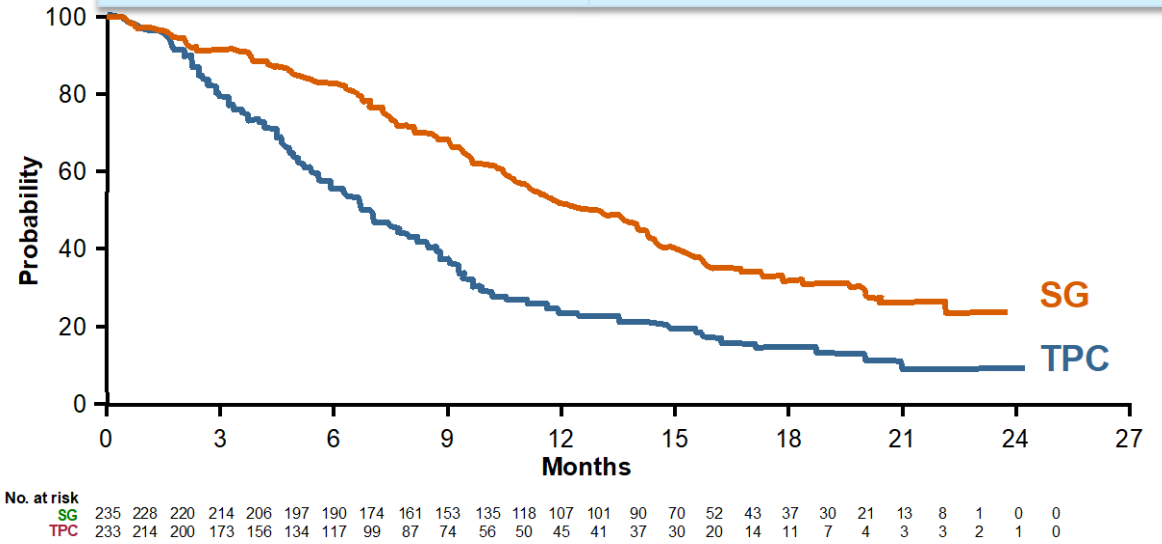
Progression-free survival

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



Overall survival

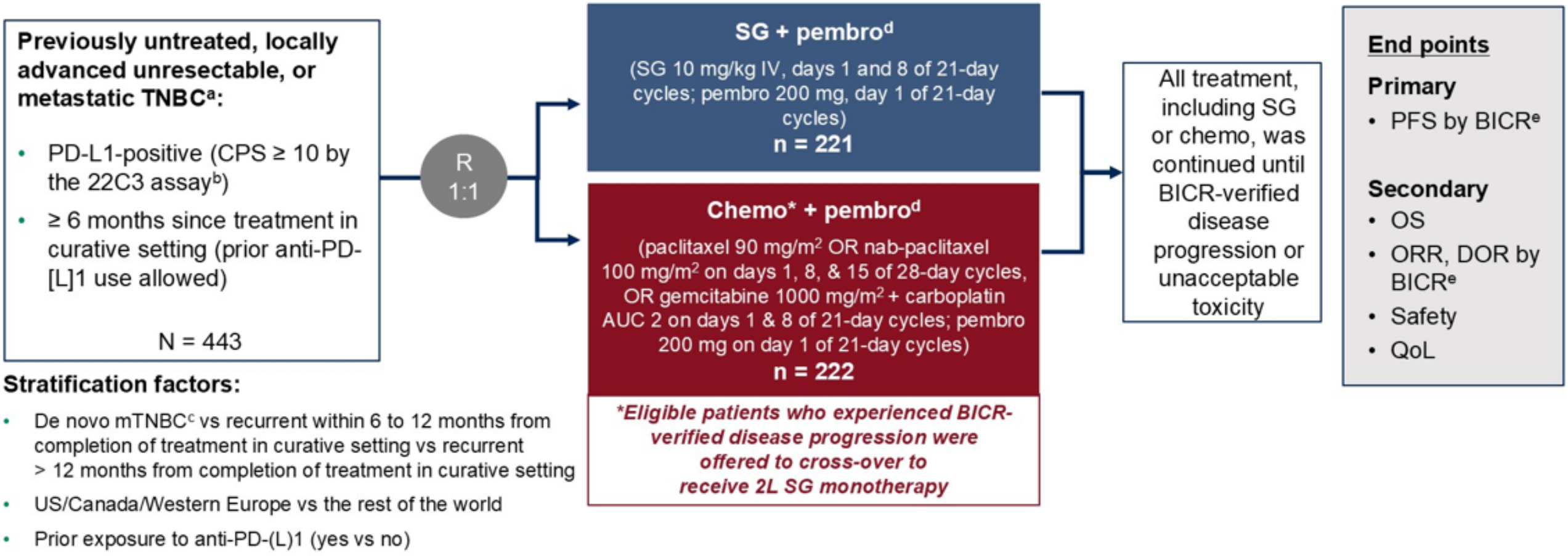
	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS, mo (95% CI)	**12.1** (10.7-14.0)	**6.7** (5.8-7.7)
HR (95% CI), P-value	**0.48** (0.38-0.59), **P < 0.0001**	



SG, sacituzumab govitecan; TPC, treatment of physician's choice.
Bardia A, et al. *N Engl J Med*. 2021; 384:1529-1541.

SG, sacituzumab govitecan; TPC, treatment of physician's choice.
Bardia A, et al. *N Engl J Med*. 2021; 384:1529-1541.

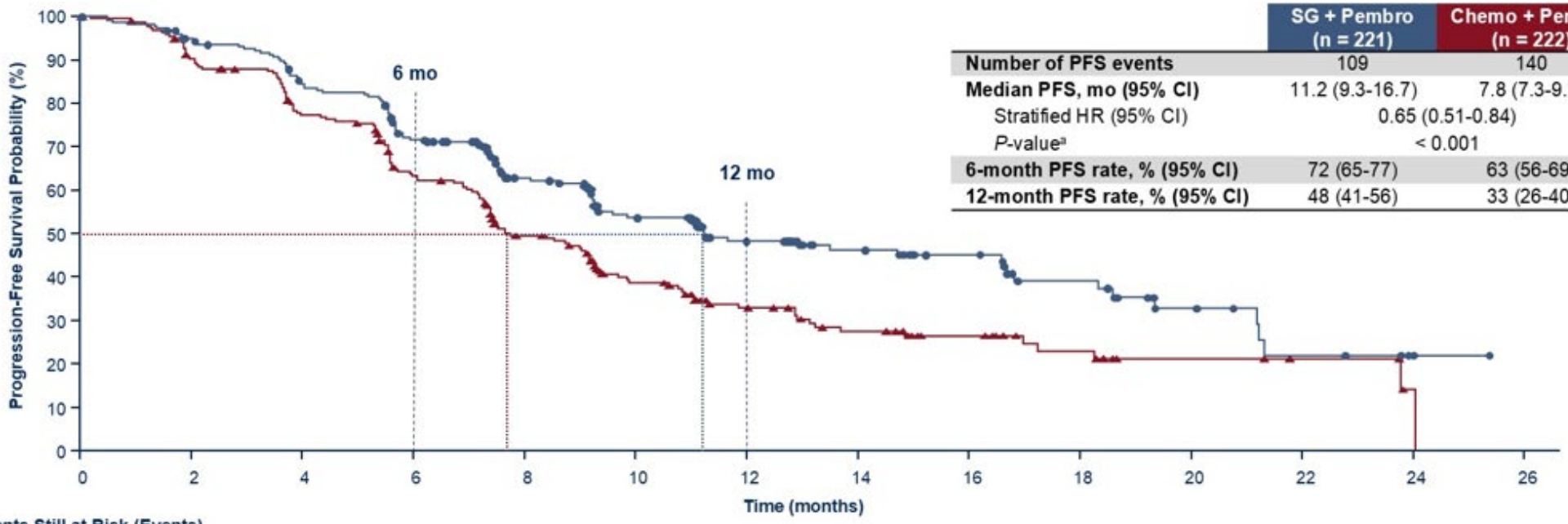
ASCENT-04/KEYNOTE-D19 Study Design



ClinicalTrials.gov identifier: NCT05382286.
[a]TNBC status determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]Dako, Agilent Technologies. [c]Up to 35% de novo mTNBC. [d]Pembro was administered for a maximum of 35 cycles. [e]Per RECIST v1.1.
AUC, area under the curve; BICR, blinded independent central review; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; QoL, quality of life; R, randomized; RECIST v1.1; Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TTR, time-to-response.

Tolaney SM et al. 2025 ASCO Annual Meeting. Abstract LBA109.

ASCENT-04/KEYNOTE-D19: Progression-Free Survival by BICR



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

No. of Patients Still at Risk (Events)

SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

Data cutoff date: March 3, 2025.
[a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; chemo, chemotherapy; HR, hazard ratio; PFS, progression-free survival; pembro, pembrolizumab; SG, sacituzumab govitecan.

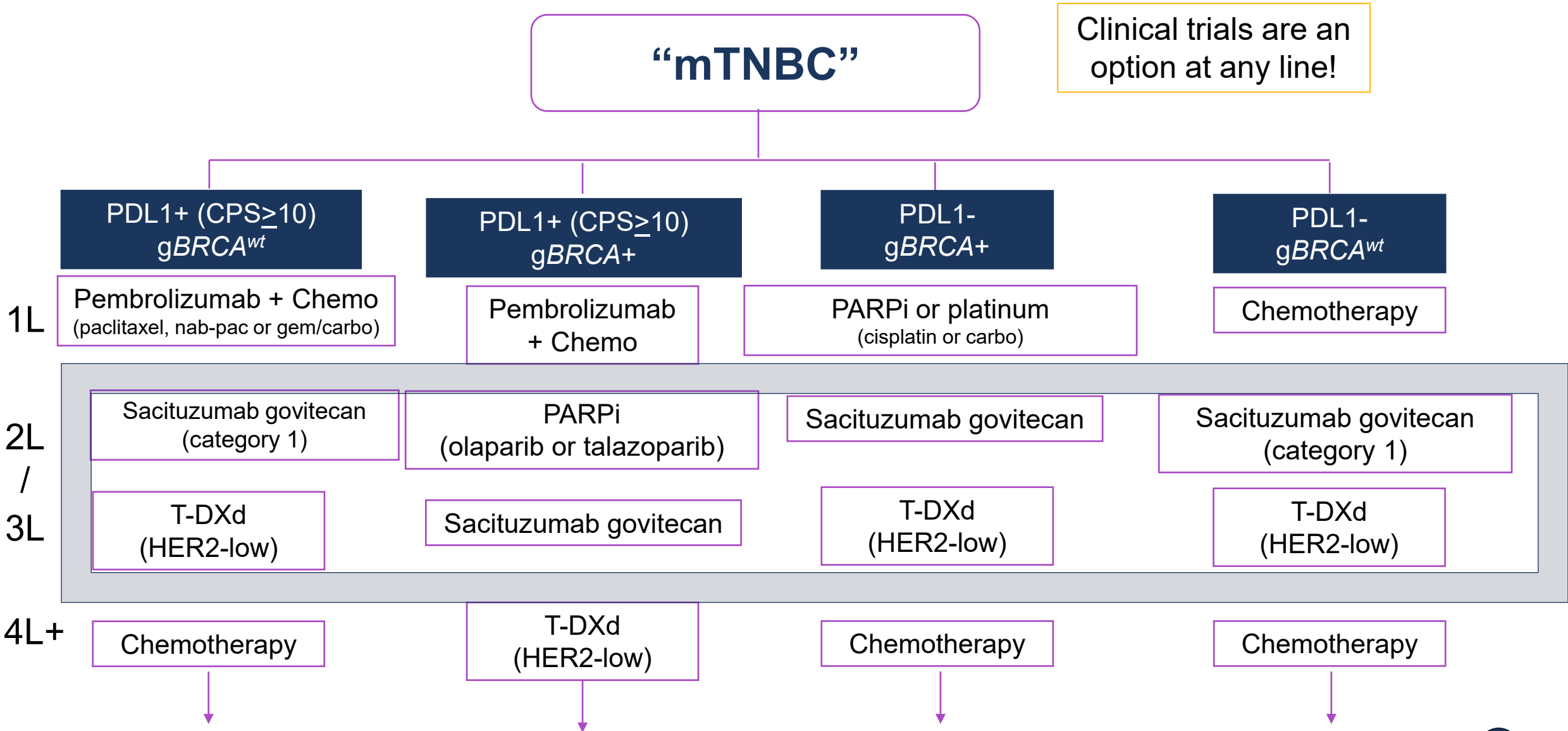
Tolaney SM et al. 2025 ASCO Annual Meeting. Abstract LBA109.

PARP Inhibitors for BRCA1/2 mutated Breast Cancer

	Approved Use	Trial	Phase	Setting	Treatment Arms	Results
Olaparib	Germline *BRCA* mutation, HER2- MBC after failure of frontline chemotherapy or hormone therapy	OlympiAD NCT02000622	3	HER2- MBC with no more than 2 prior chemotherapy regimens with a germline *BRCA1/2* mutation	A. Olaparib B. Chemo	A. **mPFS:** 7.0mo; **ORR:** 60%; **mOS:** 19.3mo B. **mPFS:** 4.2mo; **ORR:** 29%; **mOS:** 17.1mo **Hazard Ratio** – PFS: 0.58 (P < .001) OS: 0.90 (95% CI: 0.66-1.23, P = .513)
Talazoparib	Germline *BRCA* mutation with HER2- locally advanced or metastatic breast cancer	EMBRACA NCT01945775	3	Advanced breast cancer with a germline BRCA1/2 mutation	A. Talazoparib B. Chemo	**A. mPFS:** 8.6mo; **ORR:** 63%; **mOS:** 19.3mo **B. mPFS:** 5.6mo; **ORR:** 27%; **mOS:** 19.5mo **Hazard Ratio** – PFS: 0.54 (P < .001) OS: 0.85 (95% CI: 0.67-1.07, P = .17)

mPFS = median Progression-Free Survival; ORR = Overall Response Rate; mOS = median Overall Survival; CI: Confidence Interval

Robson M. et al. *N Engl J Med.* 2017; 377(6): 523-33; Robson M. et al. *Ann Oncol.* 2019;30(4): 558-66; Litton J. et al. *N Engl J Med.* 2018; 379(8): 753-63;



Adapted from NCCN v4.2025 & ESMO Guidelines.

Less common targetable alterations: NCCN v4.2025

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection[t]**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
Any	Germline *BRCA1* or *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1	Preferred
Any	Germline *PALB2*	Germline sequencing	Olaparib[y]	Category 2A	Other recommended regimen
Any	*NTRK* fusion	FISH, NGS, PCR	Larotrectinib[z] Entrectinib[z] Repotrectinib[aa]	Category 2A[aa]	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR	Pembrolizumab[bb]	Category 2A	
			Dostarlimab-gxly[cc]		
Any	TMB-H (≥10 mut/Mb)[dd]	NGS	Pembrolizumab[bb]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[ee]	Category 2A	

Fred Hutch
Cancer Center

Thank you