How I Treat Metastatic HER2+ and HER2-low BC

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July 29, 2023

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COI disclosures

RESEARCH FUNDING – ALL PAYMENTS TO INSTITUTION

- Ambrx
- Amgen
- AstraZeneca
- BIOMARIN
- Biothera Pharmaceuticals
- Clovis Pharma
- Dana Farber Cancer Institute
- Lilly
- Roche/Genentech
- G1 Therapeutics
- Gilead Sciences
- Incyte
- Innocrin Pharmaceuticals
- MacroGenics
- MedImmune
- Medivation
- Merck
- Merrimack Pharmaceuticals
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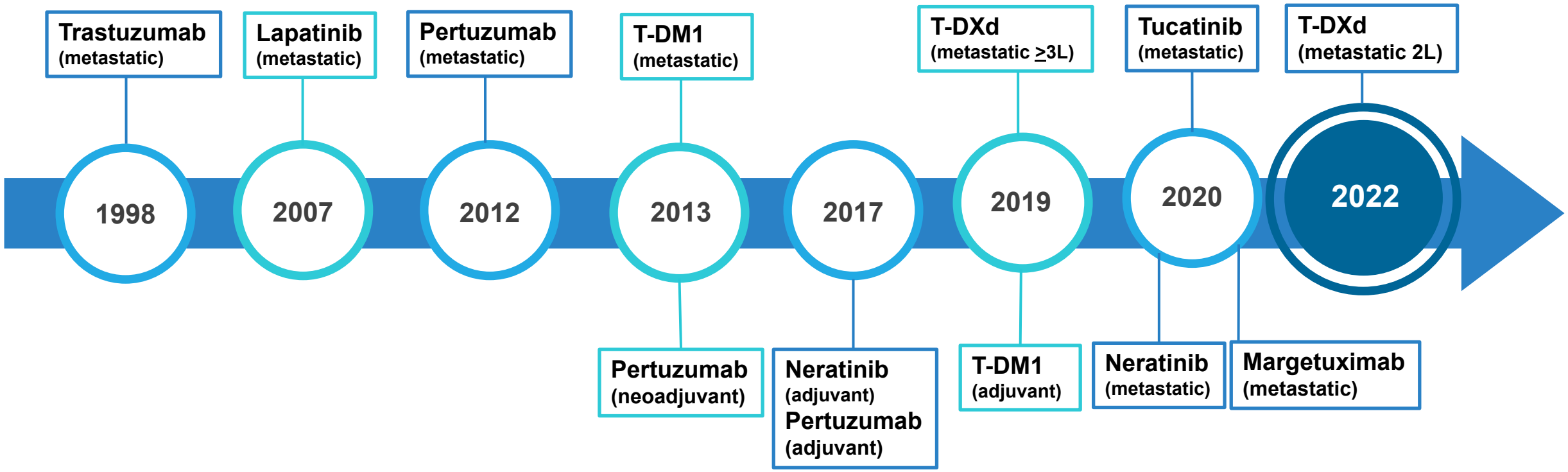
- Polyphor
- Stemline Therapeutics
- UT Southwestern

CONSULTING/ADVISORY ROLE – ALL PAYMENTS TO INSTITUTION

- AstraZeneca
- G1 Therapeutics
- Gilead Sciences
- Immunomedics
- Integra Connect
- Novartis
- Sanofi-Aventis
- Stemline Therapeutics

FDA Approved Therapies for HER2+ BC (2023)



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HER2- TKI

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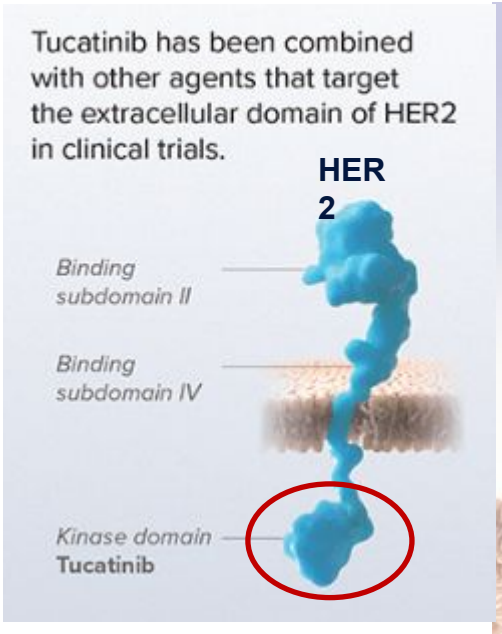
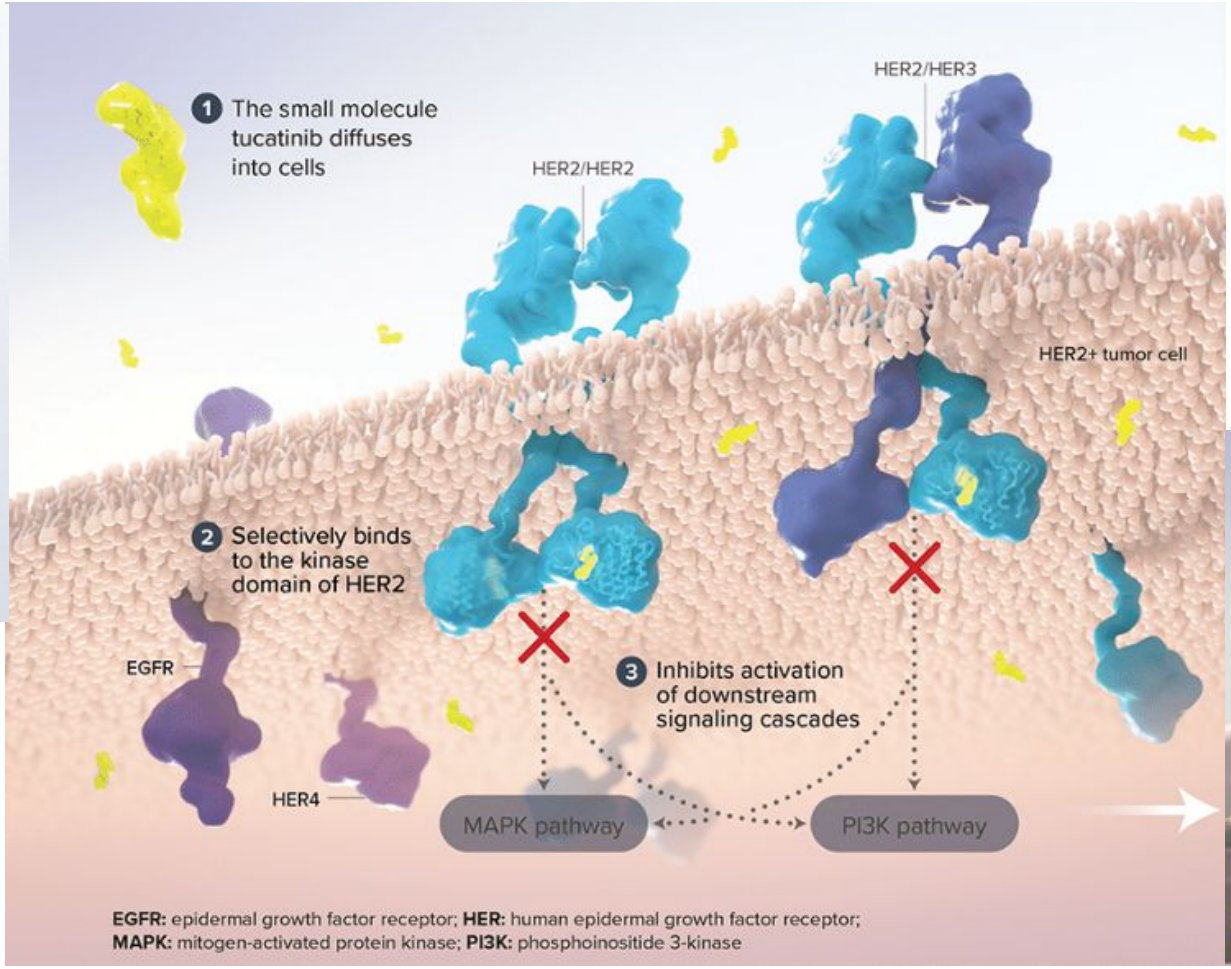
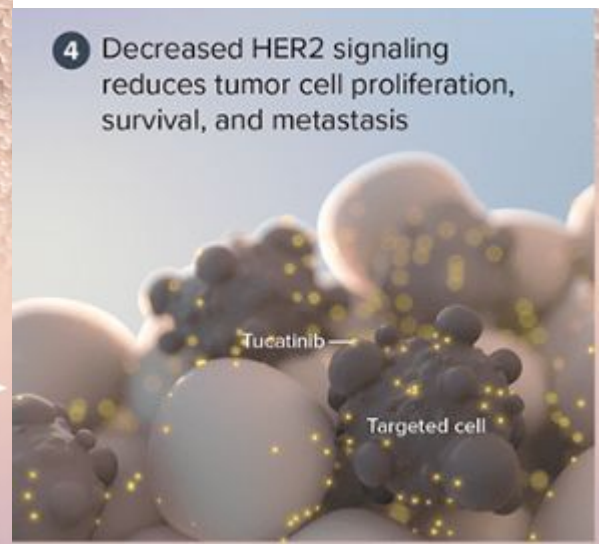
Tucatinib: Mechanism of Action

Tucatinib is a HER2-specific TKI - 1000 fold more specific for HER2 vs EGFR

Tucatinib has been combined with other agents that target the extracellular domain of HER2 in clinical trials.







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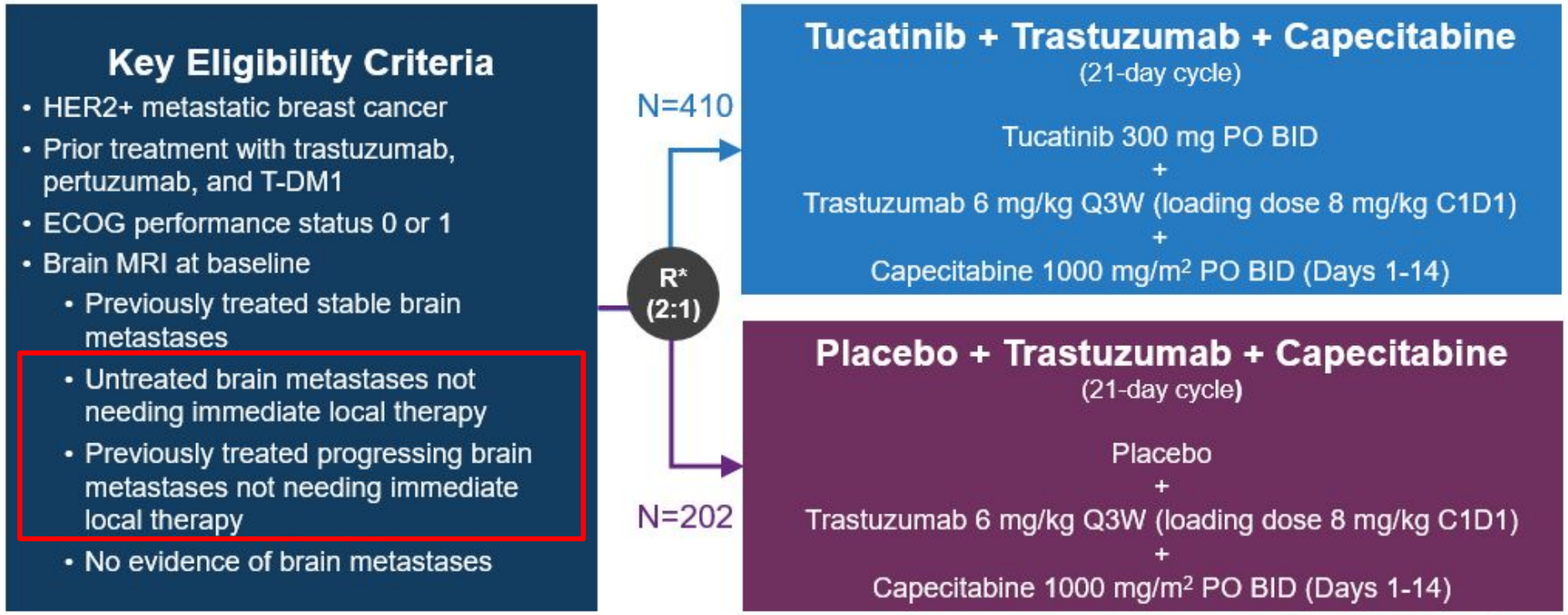
Tucatinib



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

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

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Murthy RK et al SABCS 2019, CS1-01

HER2CLIMB: Results from Primary Analysis

HER2CLIMB met all primary and secondary endpoints

PFS by BICR N=480*	Overall Survival N=612	PFS by BICR in pts with brain mets
Risk of progression or death was reduced by 46% 95% CI: 0.42 to 0.71, P<0.001	**Risk of death was reduced by 34%** 95% CI: 0.50 to 0.88, P=0.005	**Risk of progression or death was reduced by 52%** 95% CI: 0.34 to 0.69, P<0.001

PFS: progression-free survival; BICR: blinded independent central review
*The primary endpoint of PFS was assessed in the first 480 patients enrolled.

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Murthy RK et al SABCS 2019,

HER2CLIMB: CNS Benefit in Patients with Brain Metastases

	Pts with brain metastases	Pts with active brain metastases
Progression-free survival	Risk of CNS progression or death was reduced by 68% in patients with brain metastases Median CNS-PFS (95% CI): 9.9 months (8.0, 13.9) vs 4.2 months (3.6, 5.7) Δ 5.7 months	Risk of CNS progression or death was reduced by 64% in patients with active brain metastases Median CNS-PFS (95% CI): 9.5 months (7.5, 11.1) vs 4.1 months (2.9, 5.6) Δ 5.4 months
Overall survival	Risk of death was reduced by 42% in patients with brain metastases Median OS (95% CI): 18.1 months (15.5, NE) vs 12.0 months (11.2, 15.2) Δ 6.1 months	Risk of death was reduced by 51% in patients with active brain metastases Median OS (95% CI): 20.7 months (15.1, NE) vs 11.6 months (10.5, 13.8) Δ 9.1 months

Tucatinib in combination with trastuzumab+capecitabine was FDA approved on April 17, 2020 for treatment of HER2+ MBC pts (including those with brain mets)

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Murthy RK et al SABCS 2019, CS1-01

HER2- ADCs

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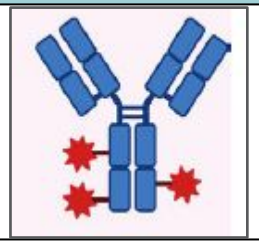
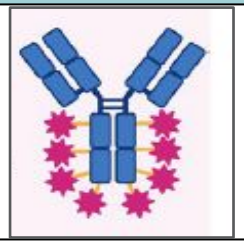
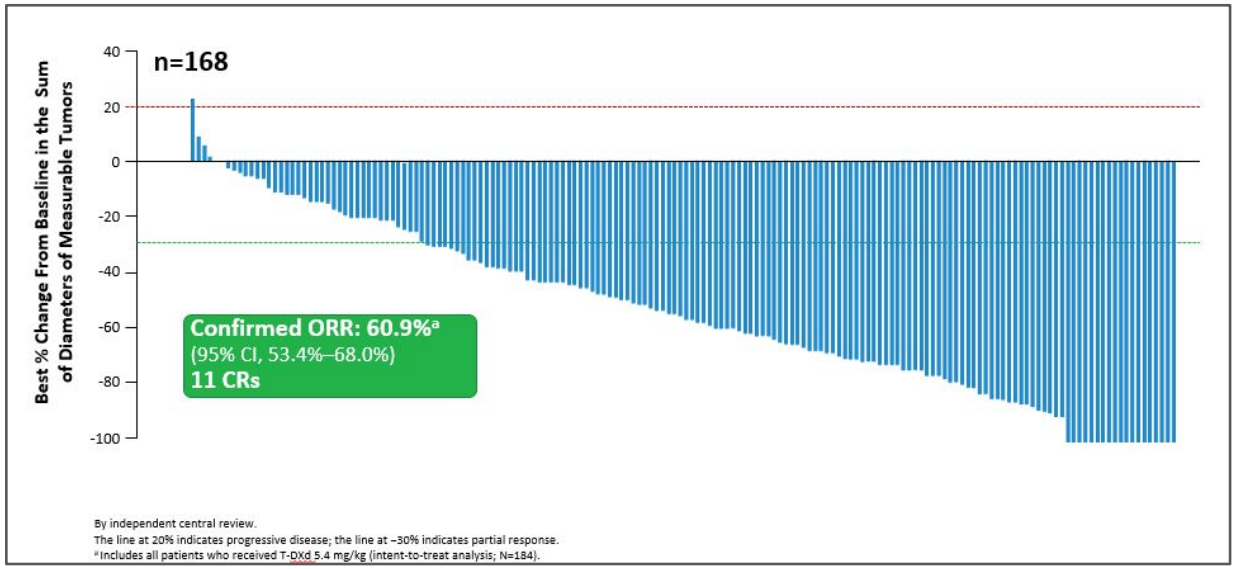
T-DM1 vs T-DXd

	Trastuzumab emtansine	Trastuzumab deruxtecan
Structure		
Antibody	Trastuzumab	Trastuzumab
Linker	Non-cleavable	Cleavable
Drug-antibody ratio	3.5:1	8:1
Cytotoxic moiety	Maytansine derivative	Exatecan derivative
MOA of cytotoxic moiety	Microtubule inhibitor	Topoisomerae 1 inhibitor
Diffusible cytotoxic moiety	No	Yes
Bystander killing effect	No	Yes
Targets HER2+ tumors	Yes	Yes
Targets HER2-low tumors	No	Yes

DESTINY Breast01: Efficacy and Safety

Phase 2 trial that evaluated T-DXd in HER2+ MBC previously treated with T-DM1

Change from baseline in tumor size



By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a]Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Confirmed ORR (by ICR):	60.9% (95% CI, 53.4%-68.0%)
Median DOR:	14.8 months (95% CI, 13.8-16.9)
Median PFS:	16.4 months (95% CI, 12.7-NE)
Most common TEAEs:	Gastrointestinal and hematologic, generally low grade and Nausea
Important identified risk:	Interstitial lung disease (ILD)

AE of special interest: ILD

	Patients who received T-DXd 5.4 mg/kg (N=184)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

Drug related; ILD was determined by the Independent ILD Adjudication Committee based on 44 preferred terms.

Among the 25 total events:

- Median time to investigator-reported onset was 193 days (range, 42-535 days)
- 17 of 20 patients with grade ≥2 ILD received corticosteroids
- 7 patients recovered, 2 were recovering, 12 were either outcome unknown or not followed until resolution, and 4 died
- Of the 4 fatal cases, onset was from 63-148 days, 3 received steroids as part of treatment, and death occurred 9-60 days after diagnosis

Recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Trastuzumab deruxtecan (T-DXd) was approved by the FDA on Dec 20, 2019 for treatment of HER2+ MBC after ≥2 prior anti-HER2 regimens

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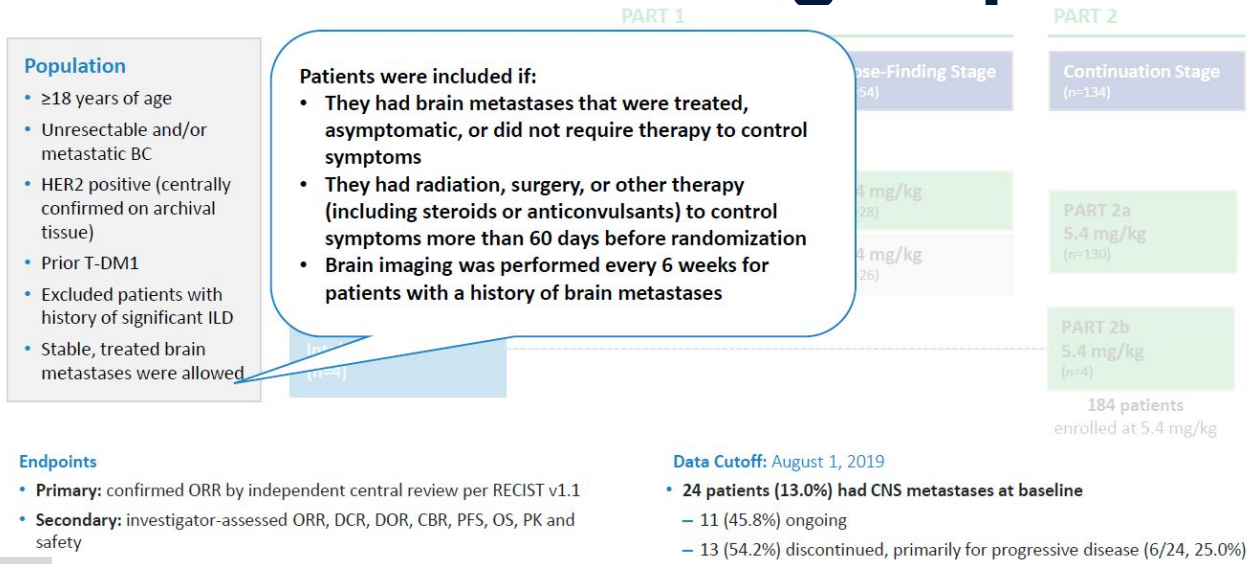
Krop I et al. SABCS 2019, GS1-03

DESTINY Breast01: CNS Metastases Subgroup



Efficacy in CNS mets subgroup

Intent-to-Treat Analysis	CNS Subgroup (n=24)	All Patients (N=184)
Confirmed ORR by ICR	**58.3% (n=14)** (95% CI, 36.6%-77.9%)	**60.9% (n=112)** (95% CI, 53.4%-68.0%)
CR	4.2% (n=1)	6.0% (n=11)
PR	54.2% (n=13)	54.9% (n=101)
SD	33.3% (n=8)	36.4% (n=67)
PD	4.2% (n=1)	1.6% (n=3)
Not evaluable	4.2% (n=1)	1.1% (n=2)
DCR	91.7% (n=22)	97.3% (n=179)
Duration of response (CR or PR), median	16.9 months (95% CI, 5.7-16.9)	14.8 months (95% CI, 13.8-16.9)
Progression-free survival, median	**18.1 months (95% CI: 6.7-18.1)**	**16.4 months (95% CI: 12.7-NE)**

T-DXd demonstrated encouraging activity in pts With HER2+ MBC and CNS mets

- Median time to response was 2.8 months (95% CI, 1.3-4.1 months) for the CNS subgroup and 1.6 months (95% CI, 1.4-2.6 months) for all patients

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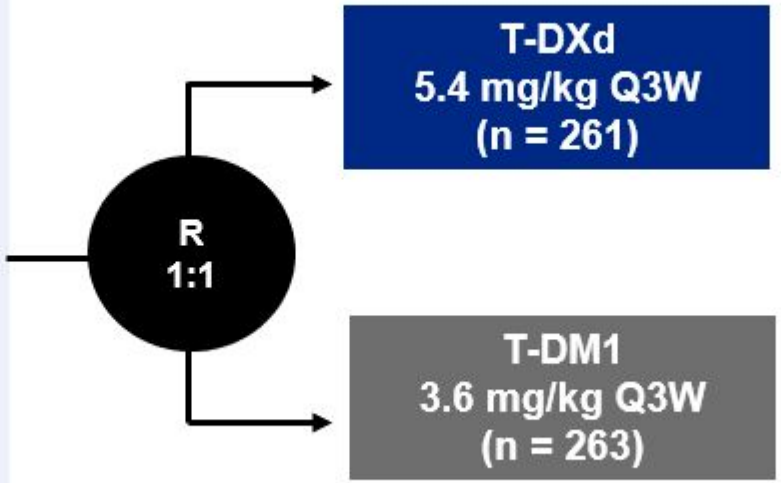
Jerusalem G et al. ESMO Breast 2020

DESTINY Breast03: Ph 3 Trial of T-DXd vs T-DM1 in 2L HER2+ MBC

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

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



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

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

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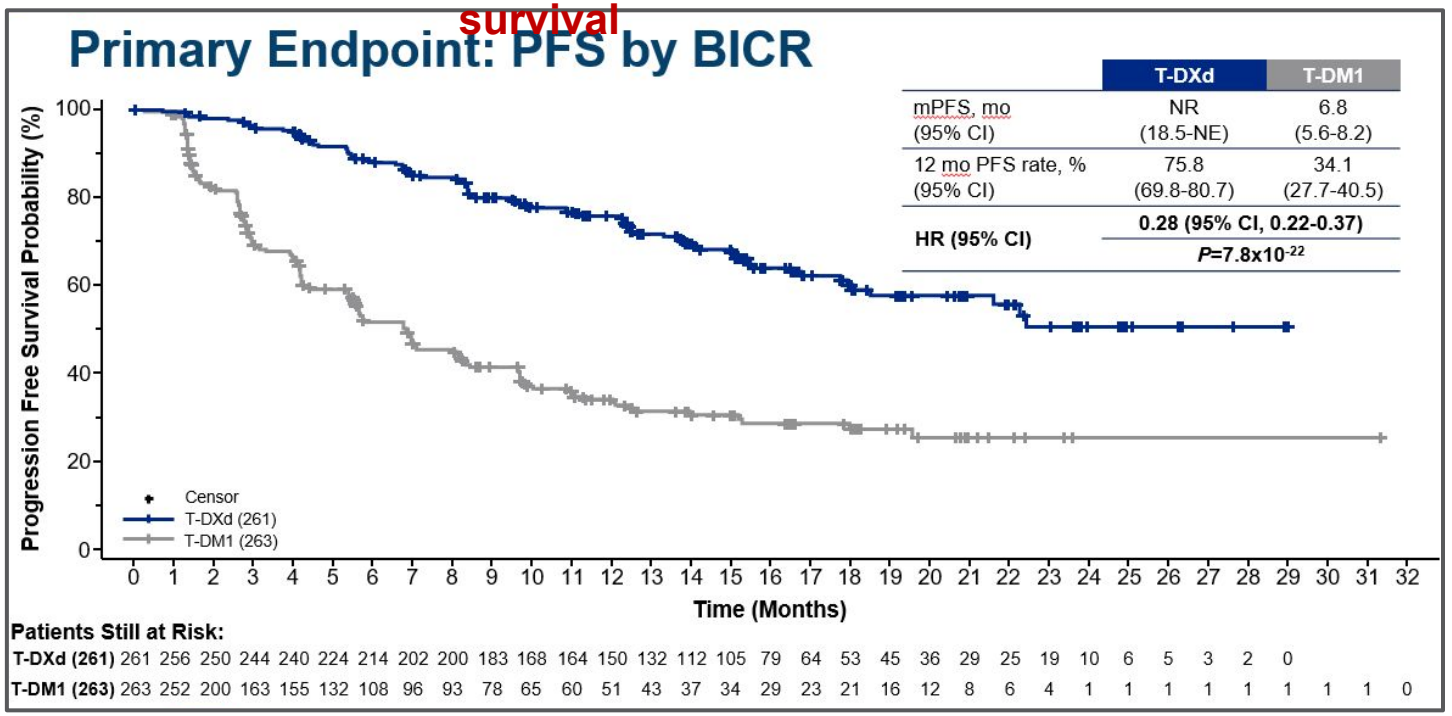
Cortes J et al. ESMO

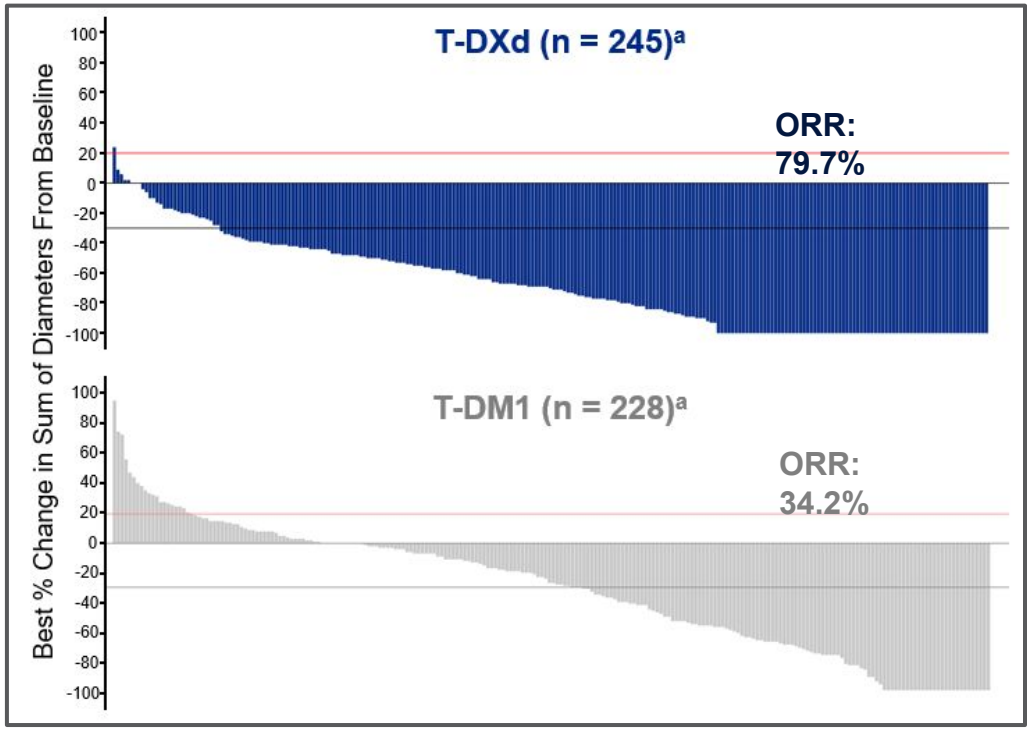
DESTINY Breast03: Efficacy Data with T-DXd vs T-DM1

Progression-free survival



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12 mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (95% CI, 0.22-0.37)	
	P=7.8x10^{-22}	

Best overall response



Statistically significant and clinically meaningful improvement in mPFS with T-DXd (not reached) compared to T-DM1 (6.8 months)

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Cortes J et al. ESMO 2021

DESTINY Breast03: Drug Related TEAEs

Drug related TEAEs reported in ≥20% of patients

	T-DXd n = 257		T-DM1 n = 261	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	189 (73.5)	17 (6.6)	72 (27.6)	1 (0.4)
Fatigue	118 (45.9)	16 (6.2)	76 (29.1)	2 (0.8)
Vomiting	114 (44.4)	4 (1.6)	15 (5.7)	1 (0.4)
Neutropenia	111 (43.2)	51 (19.8)	30 (11.5)	8 (3.1)
Alopecia	97 (37.7)	1 (0.4)	7 (2.7)	0
Anemia	82 (31.9)	16 (6.2)	37 (14.2)	11 (4.2)
Leukopenia	79 (30.7)	17 (6.6)	21 (8.0)	2 (0.8)
Decreased appetite	68 (26.5)	3 (1.2)	34 (13.0)	0
Thrombocytopenia	65 (25.3)	19 (7.4)	137 (52.5)	65 (24.9)
Diarrhea	61 (23.7)	1 (0.4)	11 (4.2)	2 (0.8)
Constipation	60 (23.3)	0	25 (9.6)	0

- Most drug related AEs were hematologic or GI related
- Any grade nausea was the most common AE with T-DXd

Hamilton E et al. ASCO

DESTINY Breast03: Safety update

n (%)	T-DXd n = 257	T-DM1 n = 261
Patients discontinued from study treatment	141 (54.9)	222 (85.1)
Any grade TEAE	256 (99.6)	249 (95.4)
Grade ≥3 TEAE	137 (53.3)	130 (49.8)
Any grade serious TEAE	54 (21.0)	50 (19.2)
Grade ≥3 serious TEAE	39 (15.2)	38 (14.6)
TEAE associated with drug discontinuation	38 (14.8)	19 (7.3)
TEAE associated with dose reduction	59 (23.0)	36 (13.8)
Treatment duration, median (range) **months**	**16.1 months**	**6.9**

- Rates of TEAEs were similar on both treatment arms
- TEAEs associated with drug discontinuation were higher on T-DXd arm (14.8% vs T-DM1 (7.3%)

Exposure-adjusted incidence rates (EAIRs)

- EAIRs per patient-year were lower in the T-DXd arm than the T-DM1 arm except for TEAEs associated with drug discontinuation, which were primarily associated with ILD/pneumonitis in the T-DXd arm
  - EAIR for grade ≥3 TEAEs was 0.42 for T-DXd and 0.70 for T-DM1
  - EAIR for any grade serious TEAEs was 0.17 for T-DXd and 0.27 for T-DM1

Hamilton E et al. ASCO 2022

DESTINY Breast03: Adjudicated Drug-related ILD/pneumonitis

	T-DXd n = 257	T-DM1 n = 261
Any grade, n (%)	28 (10.9)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	19 (7.4)	1 (0.4)
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 5	0	0
Time to first onset, median (range), days	181 (33-507)	289 (80-499)
Outcome of worst event, n (%)		
Fatal	0	1 (20.0)[a]
Not recovered/not resolved	8 (28.6)	0
Ongoing	0	0
Recovering/resolving	2 (7.1)	0
Recovered/resolved with sequelae	2 (7.1)	0
Recovered/resolved	16 (57.1)	4 (80.0)

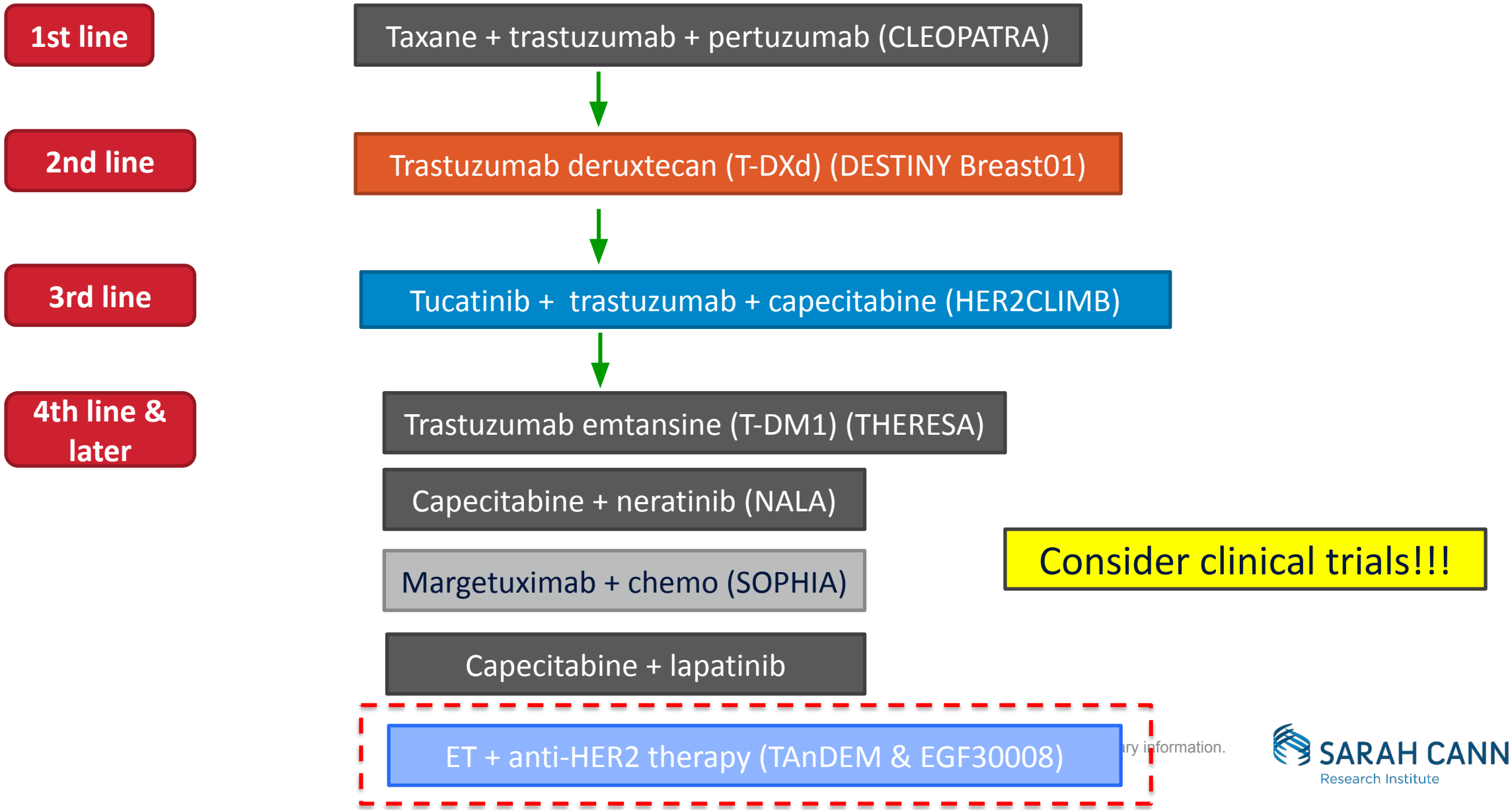
Trastuzumab deruxtecan (T-DXd) was approved by the US FDA on May 6, 2022 for treatment of HER2+ MBC after 1 prior anti-HER2 regimen for MBC or relapse ≤6 months from (neo)adjuvant anti-HER2 treatment

Hamilton E et al. ASCO

Select Ongoing Trials with Tucatinib/T-DXd for HER2+ MBC

- **DESTINY Breast07:** T-DXd combinations with chemotherapy, immunotherapy and endocrine therapy in 1-2L setting (NCT04538742)
- **DESTINY Breast09:** T-DXd +/- pertuzumab vs THP as 1L therapy for HER2+ MBC (NCT04784715)
- **DESTINY Breast12:** T-DXd in HER2+ MBC with or w/o brain mets (1-3L) (NCT04739761)
- **DASH trial:** T-DXd + ceralasertib (ATR inhibitor) for HER2+ MBC and other HER2 expressing solid tumors (NCT04704661)
- **HER2CLIMB04:** T-DXd + tucatinib for ≥3L HER2+ MBC (NCT04539938)
- **HER2CLIMB05:** Tucatinib or placebo + HP as maintenance therapy for 1L HER2+ MBC (NCT05132582)
- **TUGETHER:** Tucatinib with pembrolizumab+ trastuzumab (PD-L1+) and + cape (in PD-L1-) HER2+ MBC (NCT04789096)
- Tucatinib + gem or vinorelbine + trastuzumab for HER2+ MBC (NCT04896320)

Current Treatment Algorithm for HER2+ MBC



ary information.

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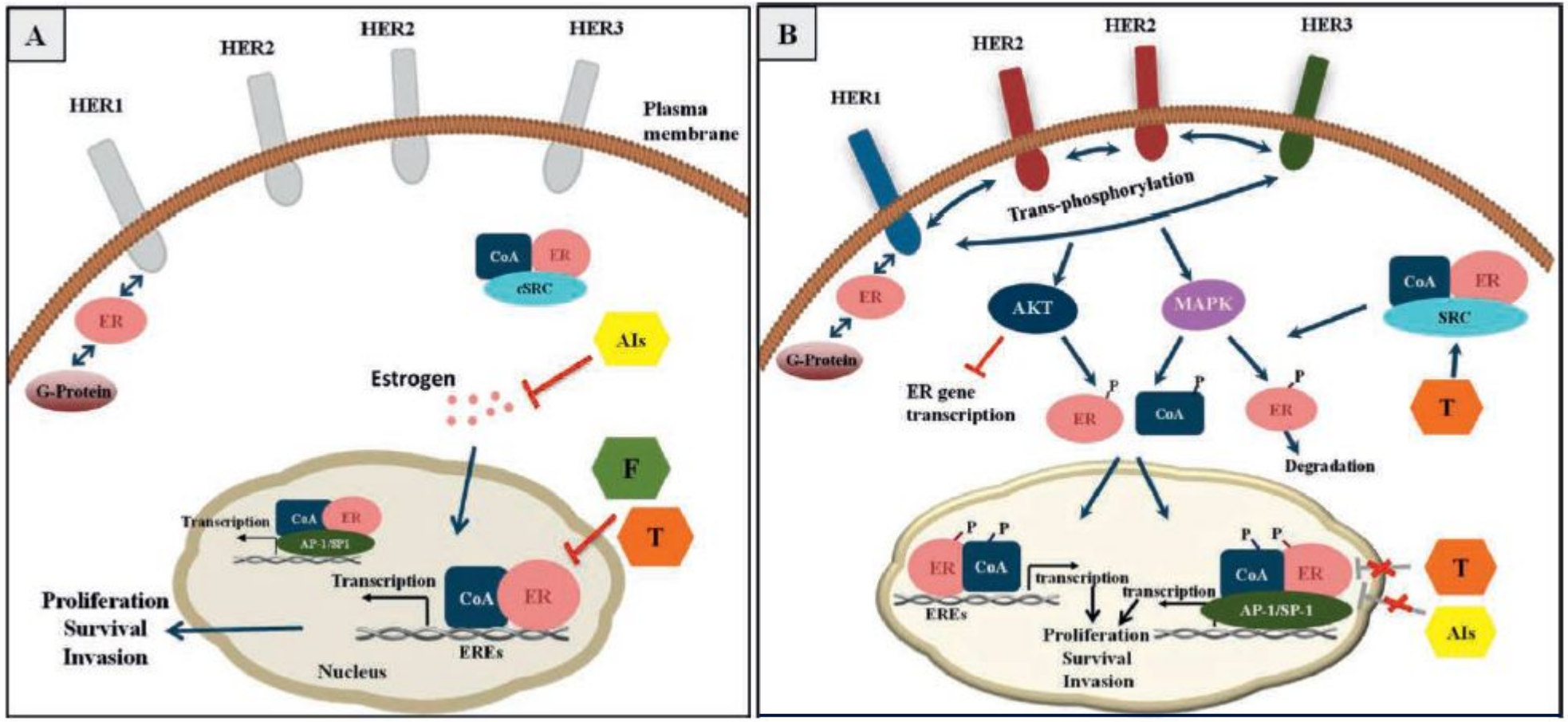
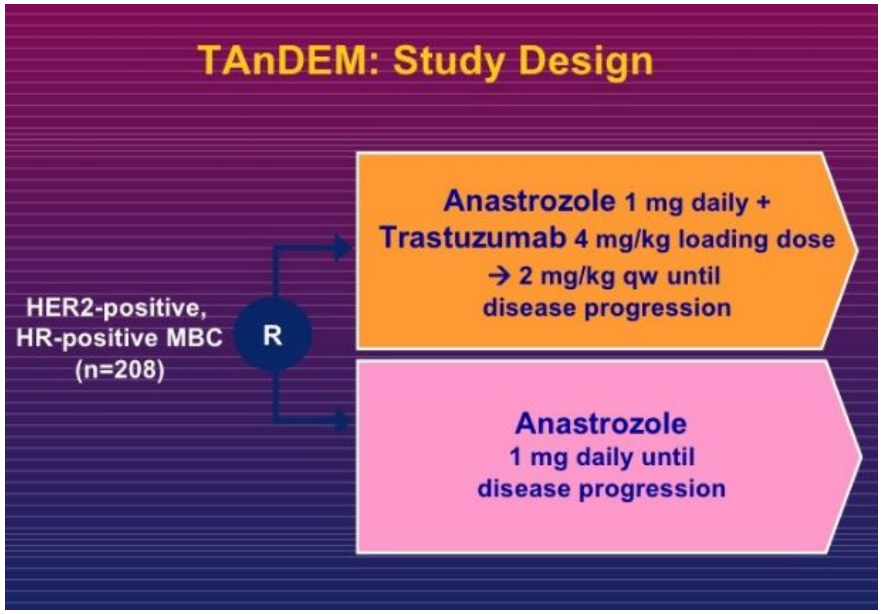
Crosstalk Between ER Signaling and HER2



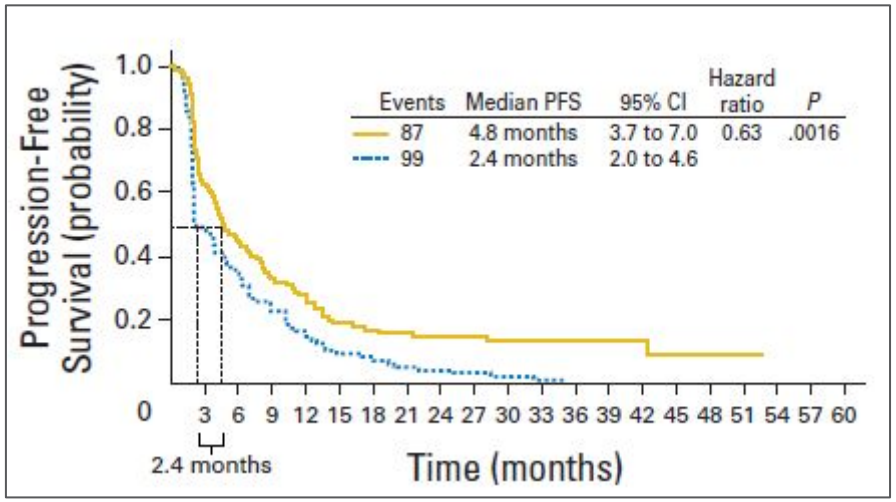
AI Aromatase inhibitor
F Fulvestrant
T Trastuzumab

Bidirectional crosstalk between the ER and HER pathways can lead to resistance to endocrine therapy

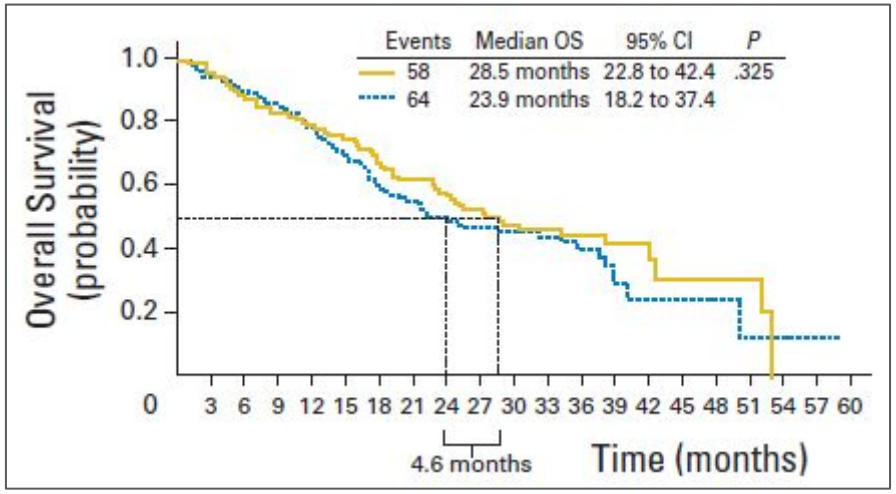
TAnDEM: 1L AI +/- Trastuzumab for HR+/HER2+ MBC



PFS (ITT)



OS (ITT)



- ✔ 1st phase 3 trial to evaluate ET with trastuzumab without chemo
- ✔ Addition of trastuzumab to ET significantly improved PFS & there was a numerical increase in OS
- ✔ G3 /4 tox were higher on trastuzumab arm, but they were reversible

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Kaufman B
et al. ICO

EGF30008: 1L Letrozole +/- Lapatinib for HR+/HER2+ MBC

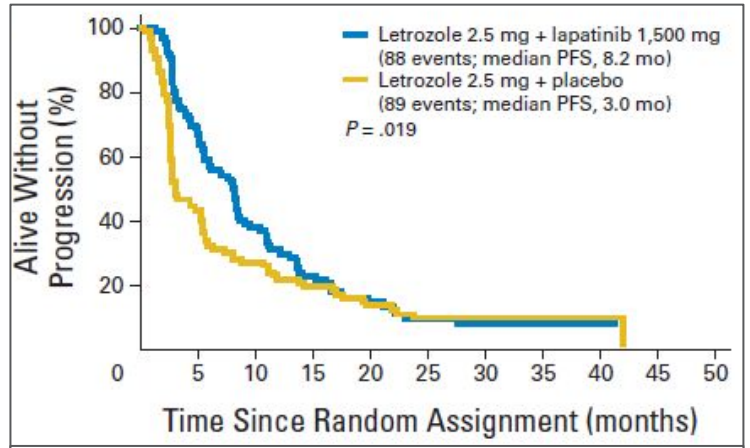
N = 219

- Pt w/ HR+ and HER2+ MBC and no prior tx for MBC were randomized 1:1
  Letrozole + placebo or Letrozole + lapatinib

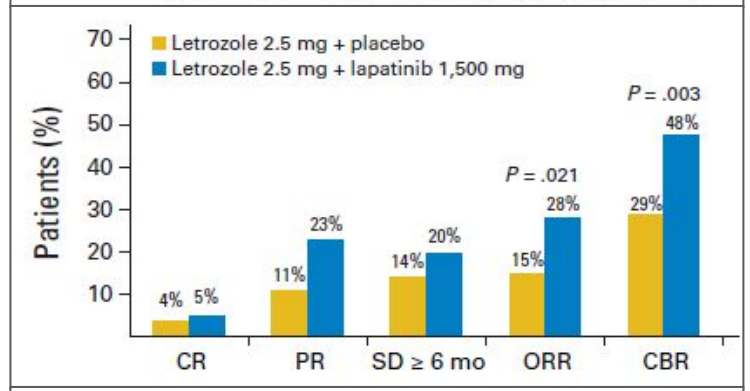
✔ Addition of lapatinib to letrozole significantly improved
  mPFS 8.2 months vs 3 months with letrozole
  ORR was 28% vs 15%
  CBR was 48% vs 29%
  Trend towards improvement in OS

✔ G3 /4 tox were higher on lapatinib arm (mainly diarrhea)

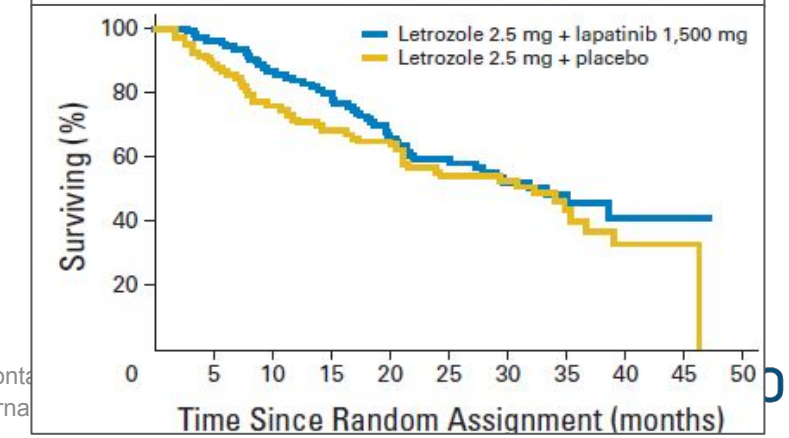
PFS



RR/ CBR

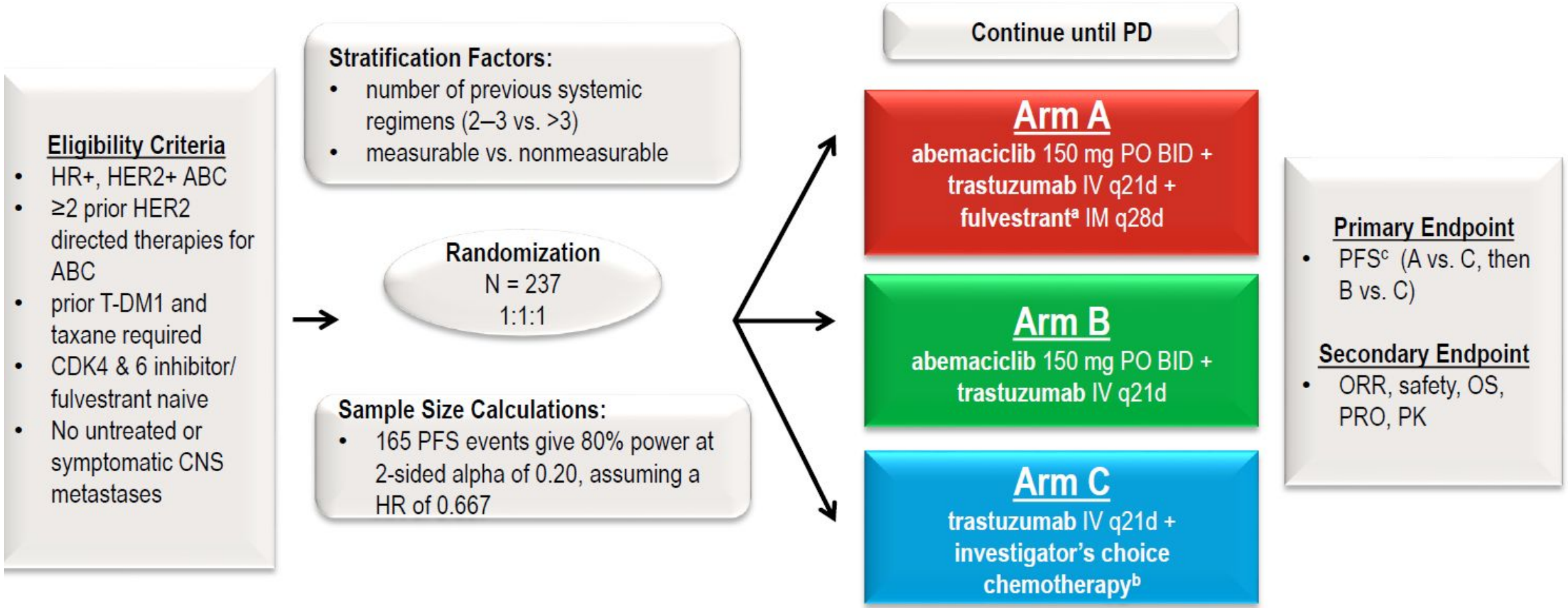


OS



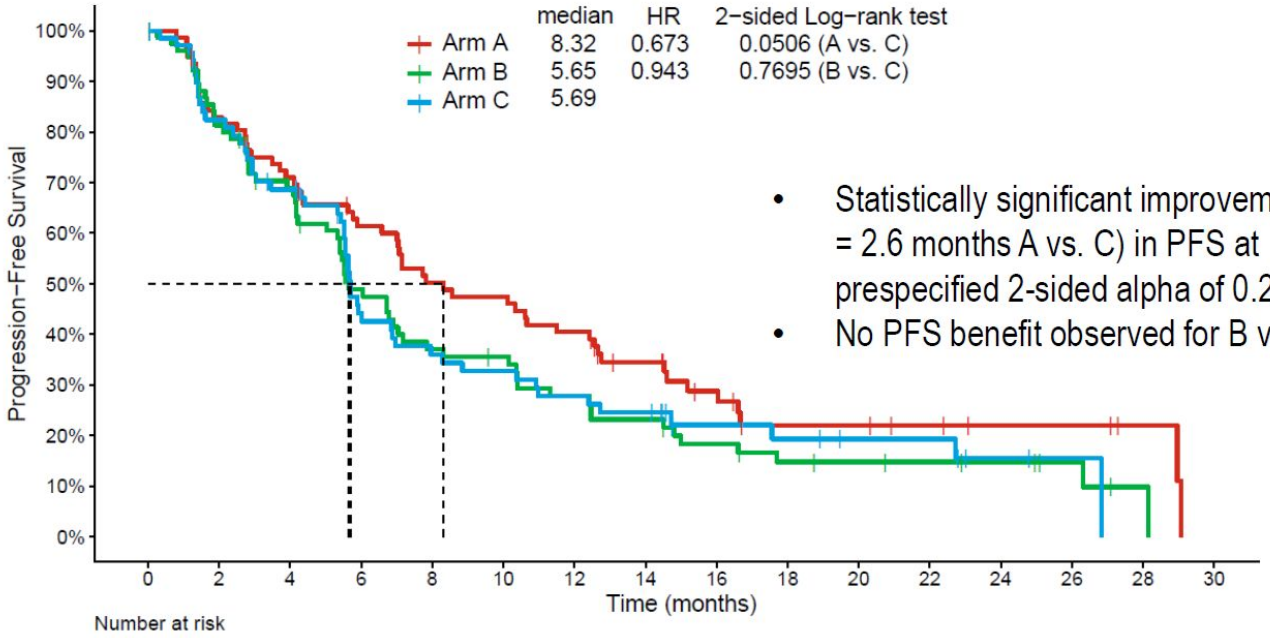
Johnston S
et al. JCO

monarcHER: Abemaciclib + ET in HR+/HER2+ MBC



monarcHER: Efficacy Outcomes

Primary EP - PFS



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

- Significant improvement in mPFS with abema+fulvestrant+trastuzumab vs trastuzumab+chemo
- Numerical improvement is OS with abema added to anti HER2 therapy + ET

Final overall survival analysis

	Arm A	Arm B	Arm C
Events	50	54	53
mOS, (mo)	31.1	29.2	20.7
HR (95% CI)	0.71 (0.48, 1.05)	0.84 (0.57, 1.23)	N/A
2-sided *P* value	0.086 A vs. C	0.365 B vs. C	
Pre-planned Final OS Analysis Data cutoff: 31 Mar 2022			

Tolaney SM et al ESMO 2019; Andre F et al. ESMO 2022

HER2-low BC

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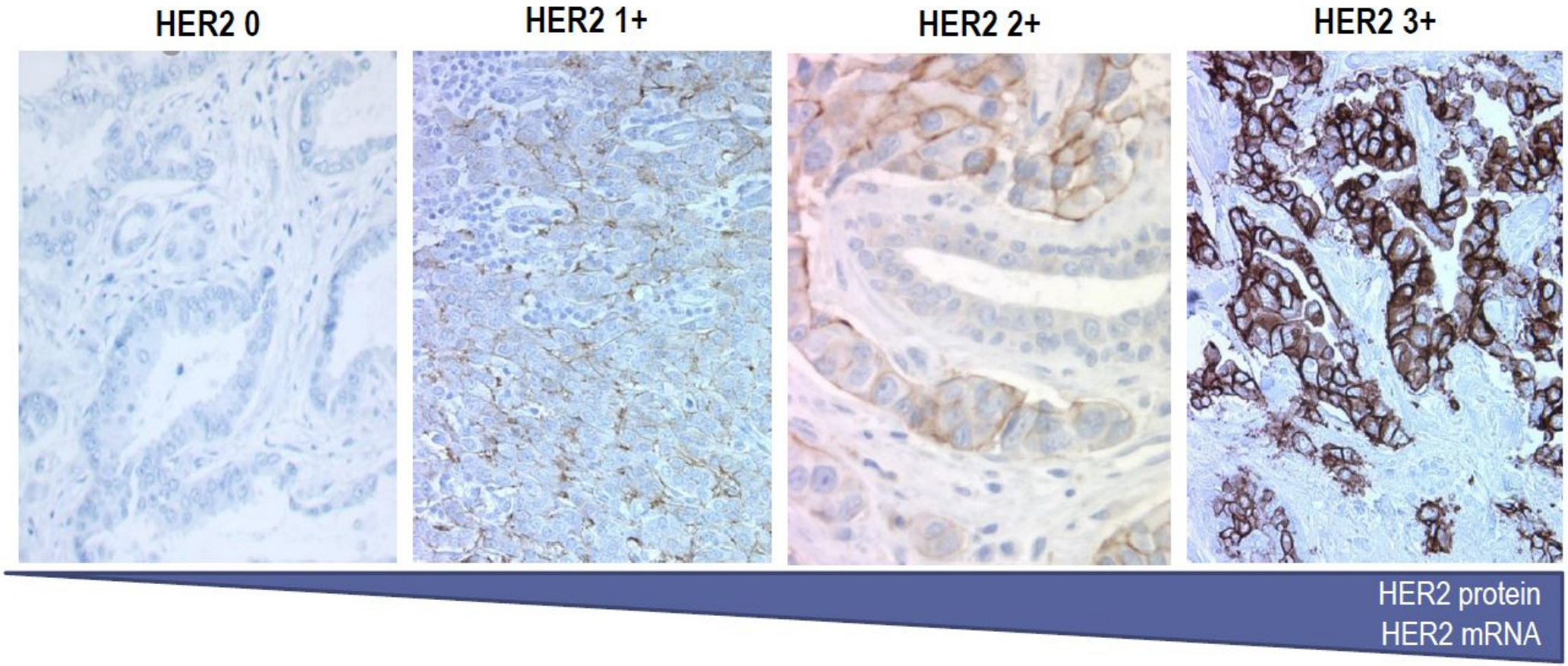
HER2: Continuum of Expression of in Breast Cancer



HER2-low

HER2 IHC 2+/ISH- OR IHC 1+/ISH – or untested

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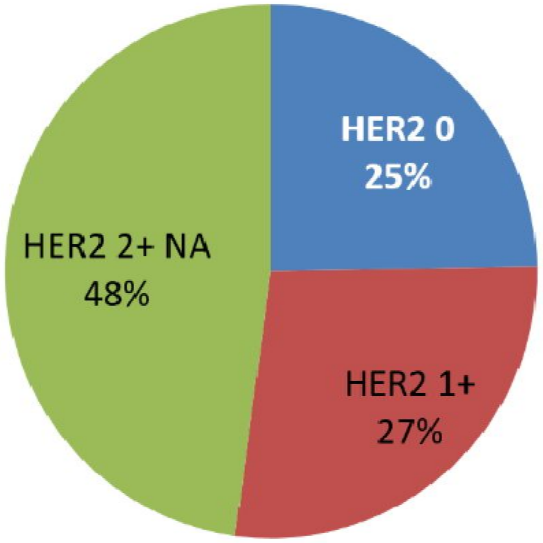
Penault-Llorca F. ESMO E-learning

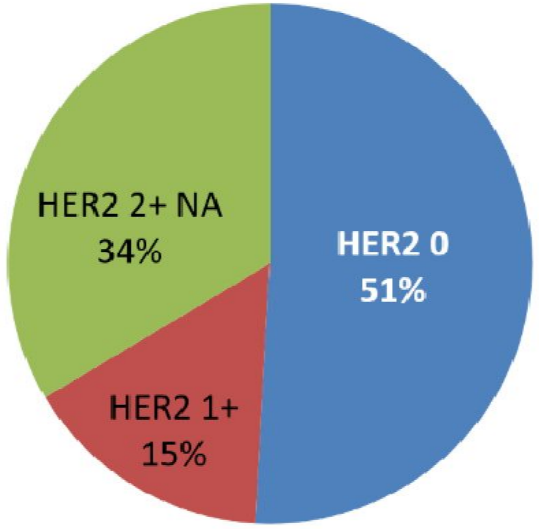
Frequency of HER2 IHC 0, 1+, 2+ in Breast Cancer

HR+ (5563 cases)



~75% HER2-low

TNBC (607 cases)



~49% HER2-low

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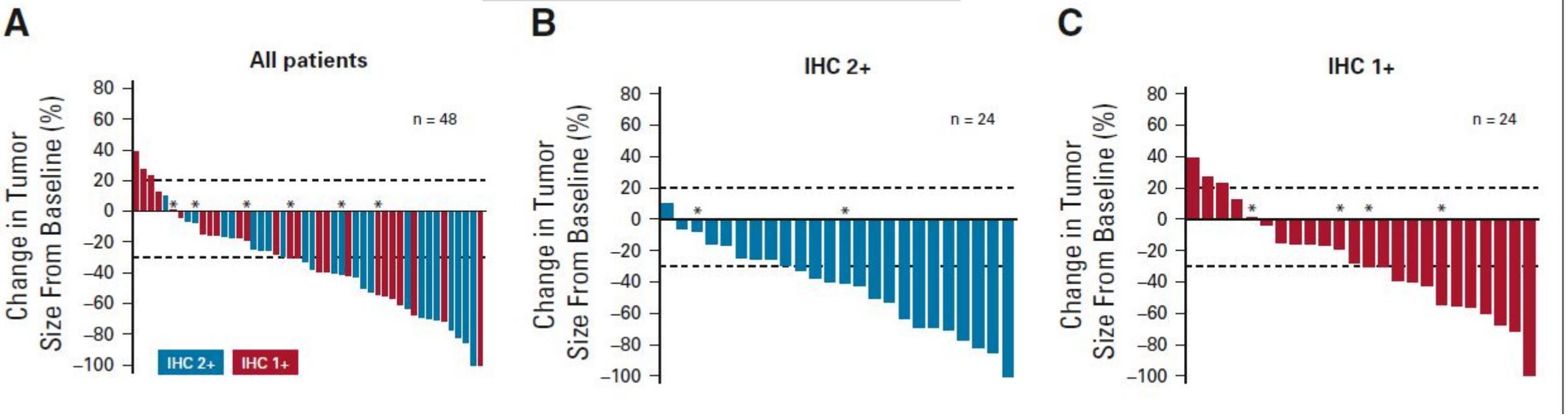
Penault-Llorca F. ESMO E-learning

T-DXd: Activity in HER2-low MBC (DESTINY Breast-01)

Best percent change in tumor size



Significant anti-tumor activity in HER2 IHC 2+ and 1+ tumors

Confirmed ORR: 37%
Confirmed DCR: 87%
Median DoR: 10.4 months
Median PFS: 11.1 months

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Modi S et al. JCO 2020

DESTINY Breast04

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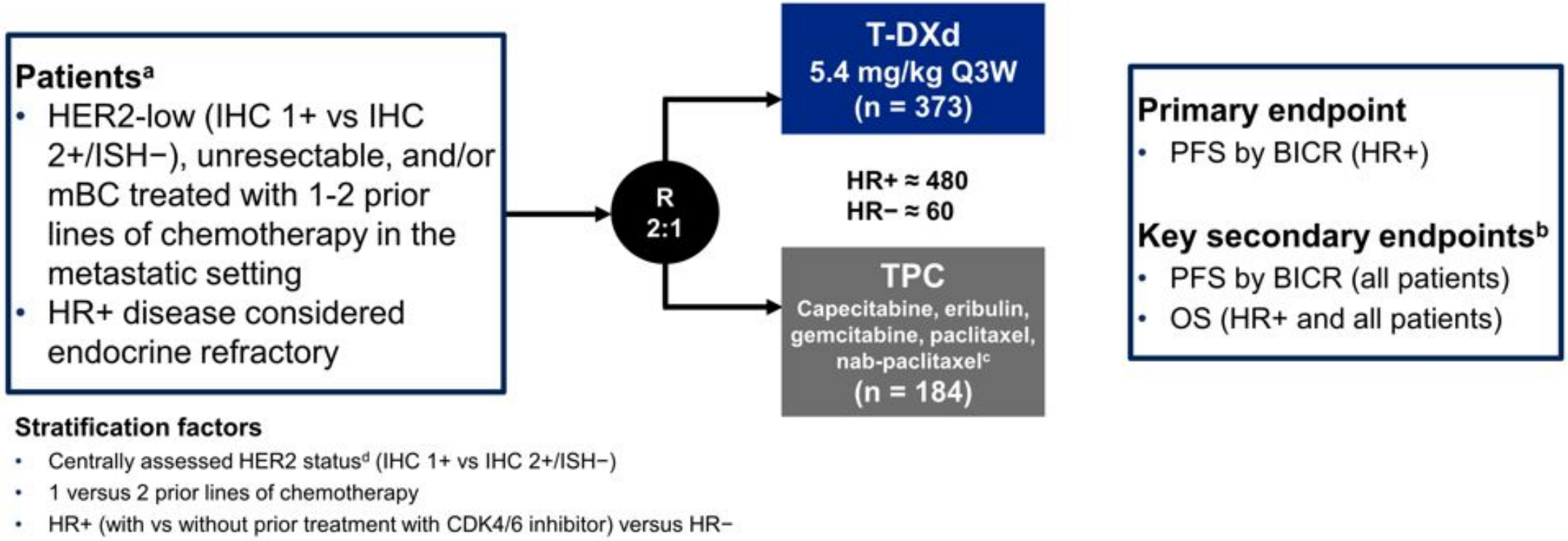
DESTINY Breast04 Schema



	Patient population HR+/HER2-low	All patients
≥3 priors for MBC	66%	62%
2 prior lines of chemo	40%	43%
Prior CDK 4/6i	70.5%	64.5%

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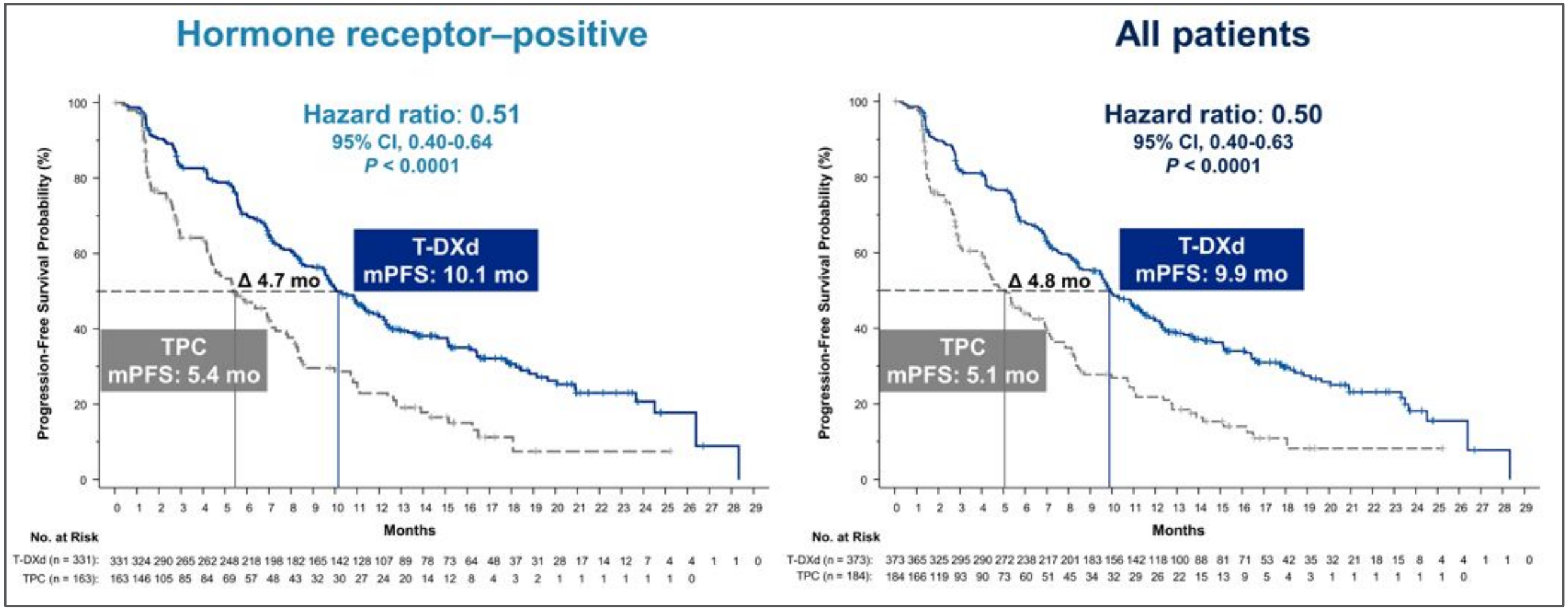
DESTINY Breast04: Progression-free Survival Primary End Point



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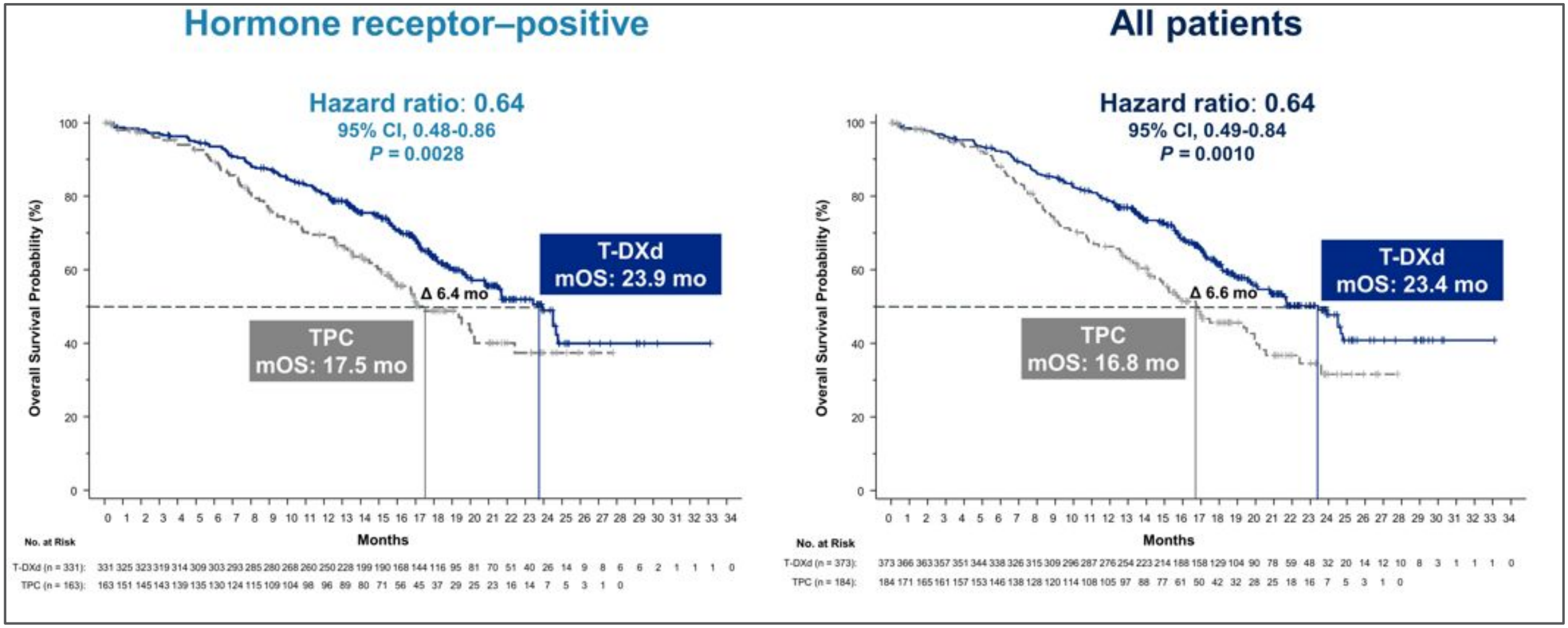
DESTINY Breast04: Overall Survival



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DESTINY Breast04:

	Overall study population (N=557)		HR+/HER2-low cohort (n=494)		Exploratory HR–/HER2-low cohort (n=58)	
	ENHERTU (n=373)	Chemotherapy (n=184)	ENHERTU (n=331)	Chemotherapy (n=163)	ENHERTU (n=40)	Chemotherapy (n=18)
mPFS (mo)	**9.9** (95% CI: 9.0, 11.3)	**5.1** (95% CI: 4.2, 6.8)	**10.1** (95% CI: 9.5, 11.5)	**5.4** (95% CI: 4.4, 7.1)	**8.5** (95% CI: 4.3, 11.7)	**2.9** (95% CI: 1.4, 5.1)
HR (*P*-value)	**0.50 (95% CI: 0.40, 0.63)** (*P*<0.0001)		**0.51 (95% CI: 0.40, 0.64)** (*P*<0.0001)		**0.46 (95% CI: 0.24, 0.89)**	
mOS (mo)	**23.4** (95% CI: 20.0, 24.8)	**16.8** (95% CI: 14.5, 20.0)	**23.9** (95% CI: 20.8, 24.8)	**17.5** (95% CI: 15.2, 22.4)	**18.2** (95% CI: 13.6, NE)	**8.3** (95% CI: 5.6, 20.6)
HR (*P*-value)	**0.64 (95% CI: 0.49, 0.84)** (*P*=0.001)		**0.64 (95% CI: 0.48, 0.86)** (*P*=0.0028)		**0.48 (95% CI: 0.24, 0.95)**	

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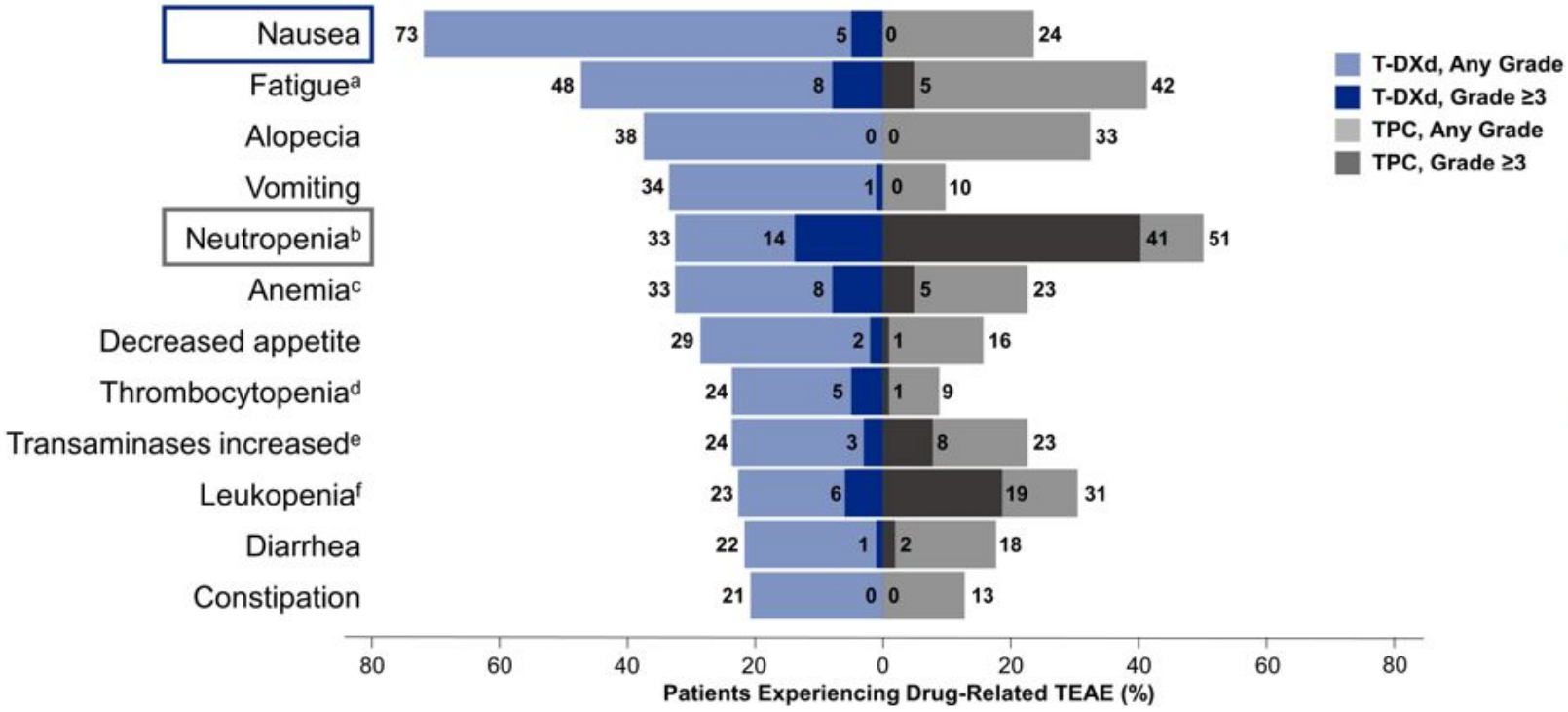
DESTINY Breast04: Adverse Events



- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy

Adjudicated as drug-related ILD/pneumonitis[a]

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

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DESTINY Breast04: Summary

- In pts with HER2-low MBC, trastuzumab deruxtecan improved
  - Median PFS by 4.8 months (HR 0.50, p<0.0001)
  - Median OS by 6.6 months (HR 0.64, P=0.0010)
  - No new safety signals; there was an overall positive benefit-risk

These results establish T-DXd as the new SOC for HER2-low MBC

T-DXd approved by the FDA for treatment of MBC for the newly defined "HER2-low" subtype on August 5, 2022

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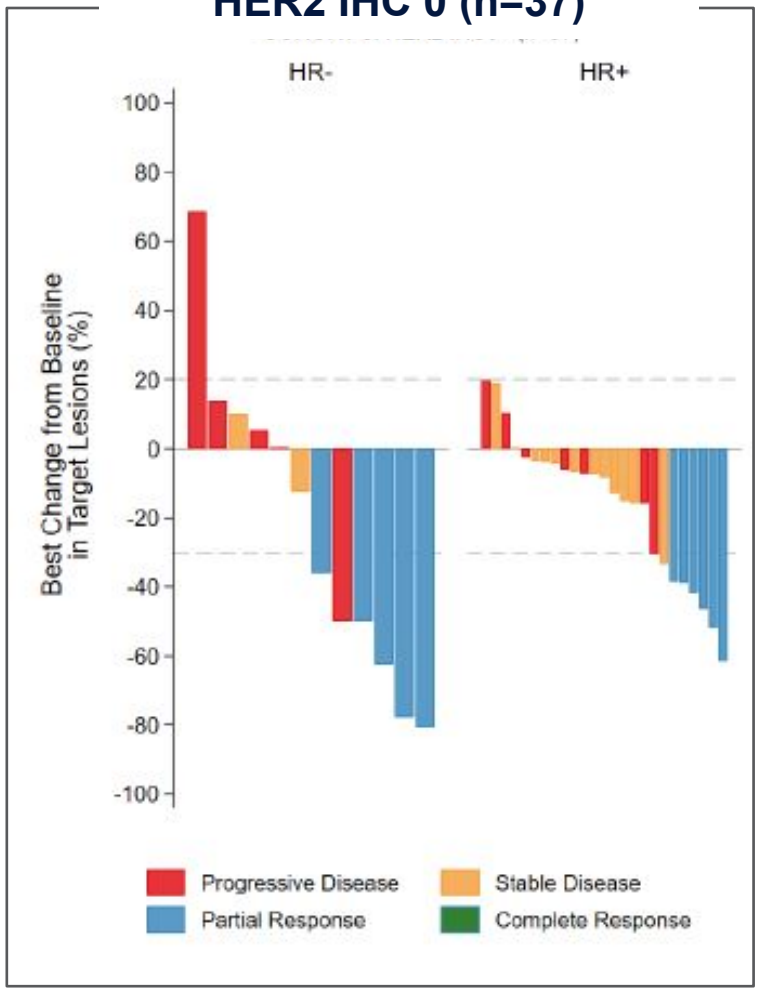
DAISY: Efficacy of T-DXd in HER2 IHC 0+(HER2 null)

- DAISY: phase 2 trial of T-DXd in HER2+, HER2-low and HER2 null MBC
- Patient population for HER2 IHC null cohort (n=38)
  - HR+: 68.4%
  - ≥3 priors: 80%

- **Confirmed ORR:** 30%
- **Median DoR:** 6.8 months
- **Median PFS:** 4.2 months

	Median PFS	Median OS
(HR+)	4.5 months	11.6 months
(HR-)	2.1 months	10.3 months

Encouraging activity with T-DXd in HER2-null MBC



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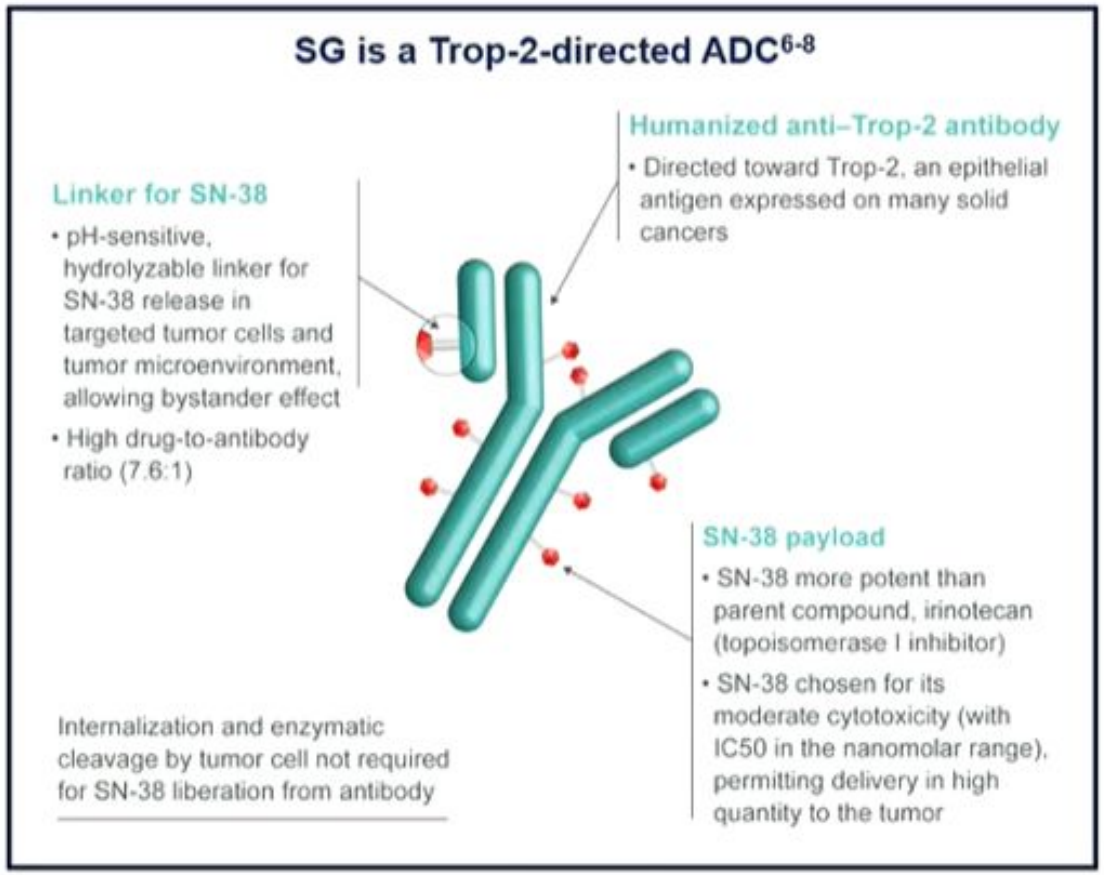
Dieras V et al. ESMO Breast 2022;

Select Ongoing Trials with Anti HER2 ADCs Enrolling HER2-low MBC

NCT04553770	T-DXd +/- anastrozole (neoadjuvant HR+ BC) (TALENT)
NCT05633979	T-DXd + Valemetostat (EZH1/2 inhibitor))
NCT05150691	DB-1303 (≥2L MBC)
NCT04257110	BB-1701 (≥2L MBC)
NCT03255070	ARX788 (≥2L MBC) (ACE Pantumor01)

Sacituzumab Govitecan (SG): Trop2 - Directed ADC in HR+/HER2- MBC



- Phase 3 **TROPICS-02** evaluated SG vs TPC in HR+/HER2- MBC
  - Significant improvement in mPFS with SG (HR 0.66, P<0.001)
  - Significant improvement in OS with SG (HR 0.79, P=0.020)
  - A posthoc subgroup analysis evaluated efficacy in the HER2-low subgroup

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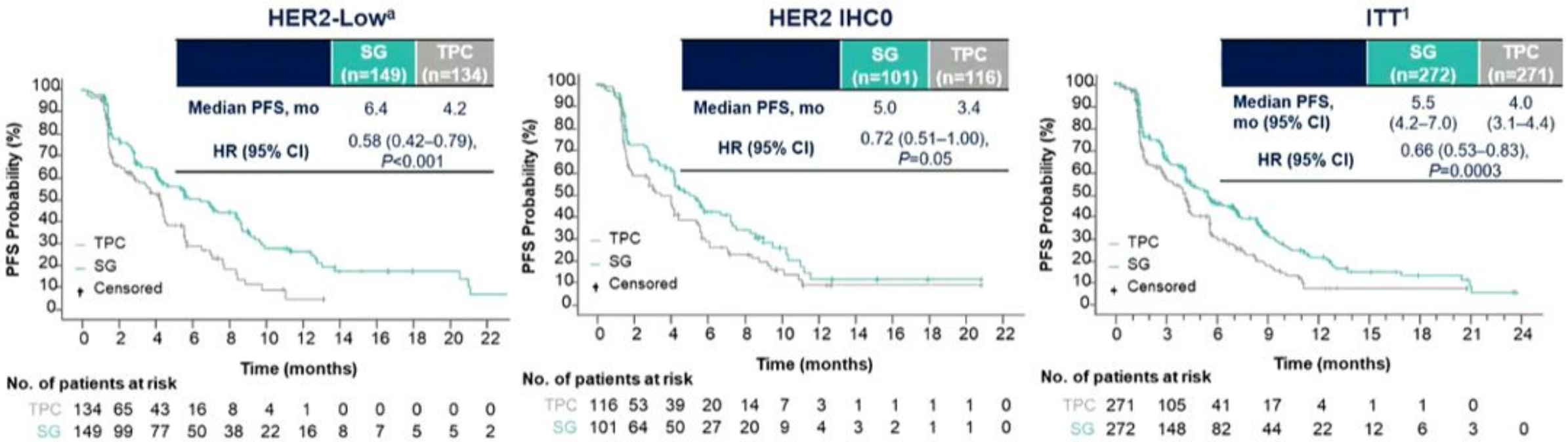
Marme M et al. ESMO 2022

SG Improved Outcomes in HR+ ER2-low & HR+ HER2 IHC 0

Post-hoc analysis: Progression-free survival



- Within the HER2-low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 months (HR, 0.57) and 5.6 vs 4.0 months (HR, 0.58), respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

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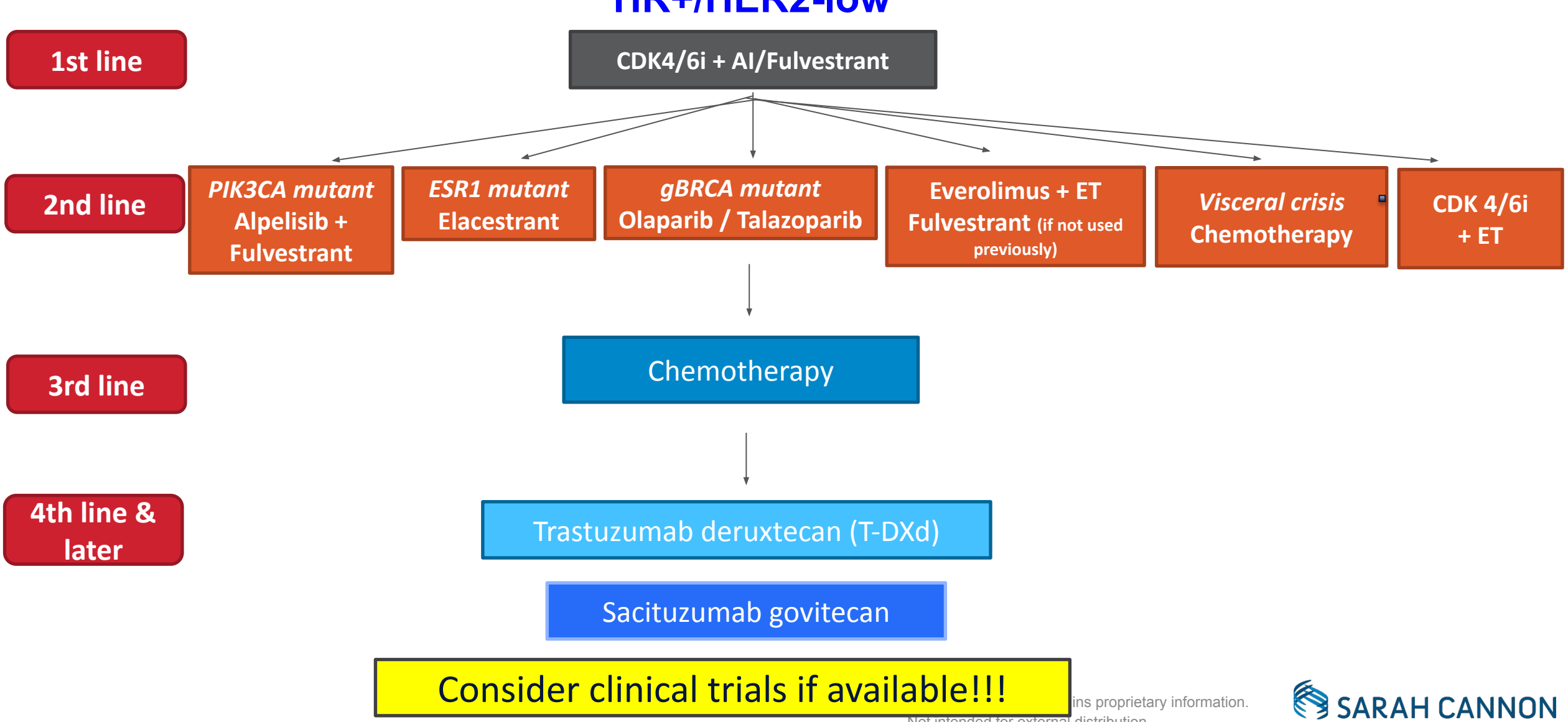
Marme M et al. ESMO 2022

Current Treatment Algorithm for HR+ HER2-low MBC



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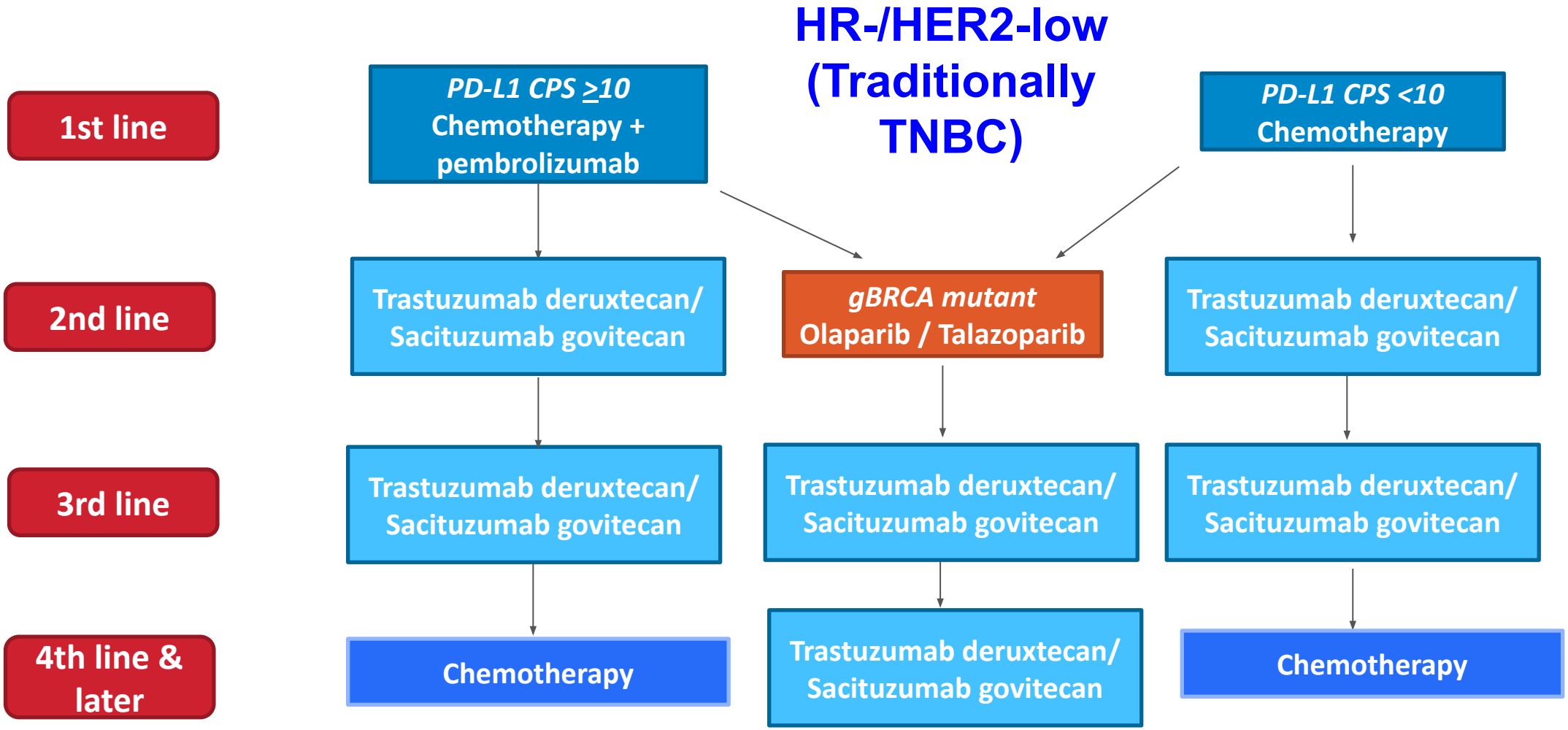
Current treatment algorithm for HER2-low MBC



Consider clinical trials if available!!!

ry information.

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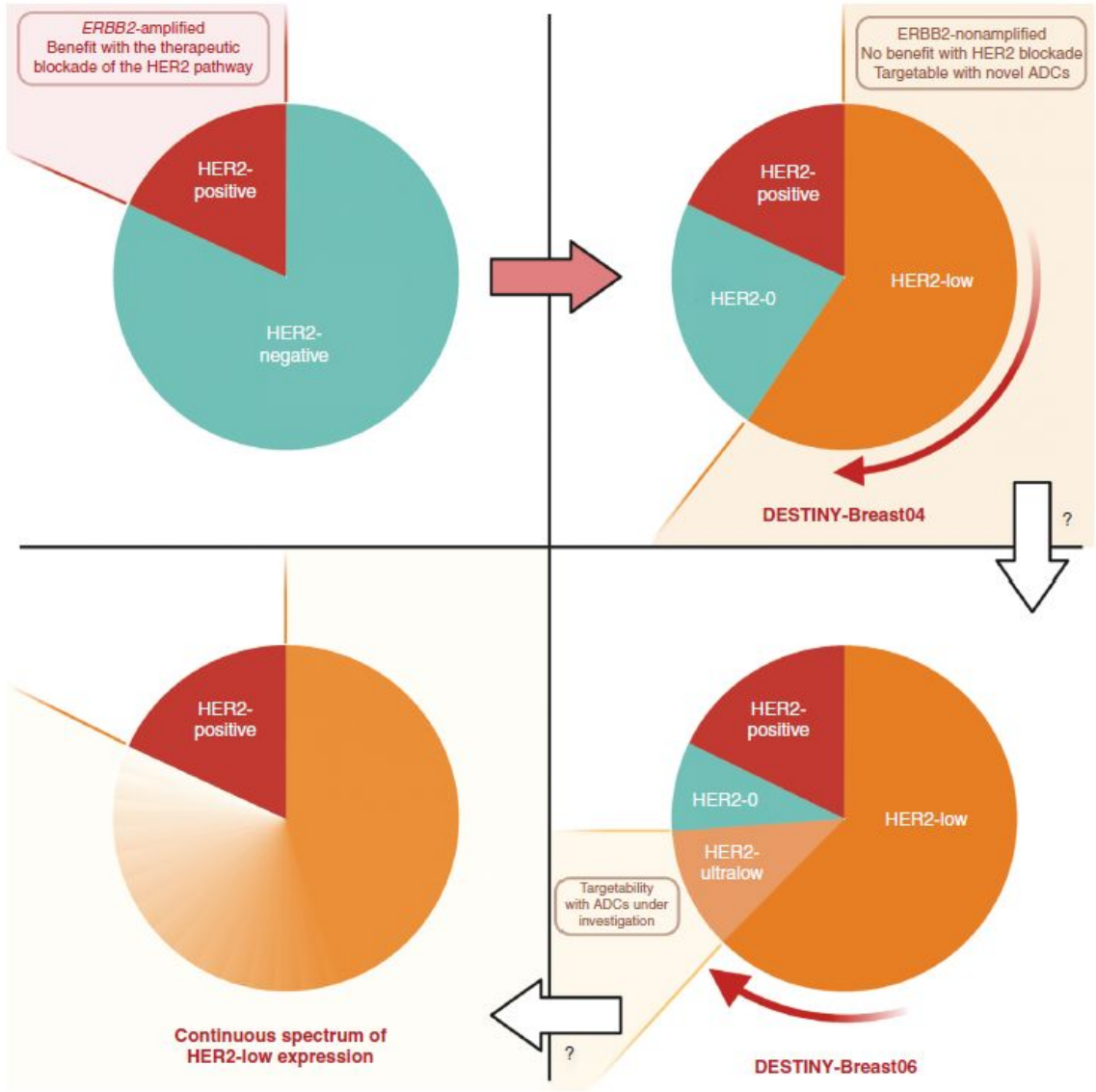
Evolving categorization of HER2-low



Shift from a binary categorization of “yes” or “no” to HER2-positive, HER2-low and HER2-0

May undergo further evolution with HER2-“ultralow”

Development of more quantitative HER2 evaluation methods

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Tarantino P et al. Cancer Discov 2022

Thank You

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