CHALLENGING CASES

HR+ Breast Cancer

Prepared by: Cornerstone Specialty Network

Challenging Cases Conducted: August 8, September 4, October 2, October 7, October 14, November 12, December 3, 2025

Participating Practices

Challenging Cases in…
Breast Cancer

Program conducted:

August–December 2025

Note: Aggregated results and high-level summary based on 6 practices and 1 Live Regional Exchange (53 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

• **Live Leadership Exchange SLC (n=12)**	**August 8, 2025**
• **Zangmeister Cancer Center (n=6)**	**September 4, 2025**
• **Maryland Oncology Hematology (n=4)**	**October 2, 2025**
• **Ironwood Cancer & Research Centers (n=7)**	**October 7, 2025**
• **Cancer Center of Kansas (n=5)**	**October 14, 2025**
• **Fort Wayne Oncology & Hematology (n=8)**	**November 12, 2025**
• **Northwestern Medicine (n=11)**	**December 3, 2025**

Overall Program Impact and Future Considerations

Community oncologist favor trastuzumab + pertuzumab + taxane or trastuzumab deruxtecan (T-DXd) as first-line therapies for HR+ HER2+ metastatic breast cancer depending on timing of relapse, with some reserving T-DXd for later lines due to ILD risk; DB09 and PATINA show promising PFS benefits, while sequencing, endocrine therapy timing, and safety considerations drive decision-making with emerging trial data shaping future adoption strategies on FDA approval

- **Front-line strategy:** Trastuzumab + pertuzumab + taxane is generally preferred regimen for *de novo* metastatic disease or relapse >12 months post-neoadjuvant therapy, while some favor trastuzumab deruxtecan (T-DXd); some reserve T-DXd for later lines due to ILD risk and comorbidities
- **Toxicity considerations:** ILD risk with T-DXd and CDK4/6i–related neutropenia or fatigue with PATINA are the main safety concerns influencing sequencing decisions and patient selection
- **Endocrine therapy:** ET is added during HER2 maintenance after taxane discontinuation in THP regimens. Timing with T-DXd is variable —some clinicians add it upfront, others after several month; it was noted that PATINA regimen integrates endocrine therapy early with palbociclib
- **Sequencing:** Clinicians emphasize sequencing over a single “best” regimen, aiming to use all effective agents across lines. Most currently reserve T-DXd for 2L+ while optimizing HER2-targeted and endocrine combinations upfront. PATINA and DESTINY-Breast09 data are influencing future sequencing strategies, though OS data remain immature
- **Future direction:** The treatment landscape is evolving rapidly with PATINA and DESTINY-Breast09 showing significant PFS improvements over CLEOPATRA. If approved, these regimens will compete for 1L adoption, with uptake driven by efficacy, safety, and clinician familiarity
- ***Recommended actions:*** *Expand education through Challenging Cases and evidence-generation initiatives leveraging CSN Clinical Investigations to clarify optimal sequencing and timing of endocrine therapy, patient selection for T-DXd and DESTINY-BREAST09 vs PATINA, management of safety concerns to integrate of emerging therapeutics into real-world practice*

Challenging Cases in Breast Cancer

HER2-positive Breast Cancer

Patient Case: 1st line mBC

- *Awareness of current clinical trial data and impact on treatment decisions?*
- *What impact will new clinical data have on your treatment decisions?*

1st-line mBC Therapy Decision

Patient History

69-year-old

Hypertension; Non-smoker

Initial diagnosis:

October 2022

Initial treatment:

Neoadjuvant TC-HP followed by surgery - which showed no pCR,

then treated with one year of T-DM1

Metastatic Diagnosis

December 2023:

Developed mets to liver after completing post neoadj, then T-DM1 after 1 year

IHC 3+

ER +: 80%

PR+: 20%

PD-L1: CPS 30

ECOG PS 1

What is your treatment recommendation for HR+, HER2+ mBC after post neoadj. TC-HP and adj. T-DM1?

(polling options on next slide)

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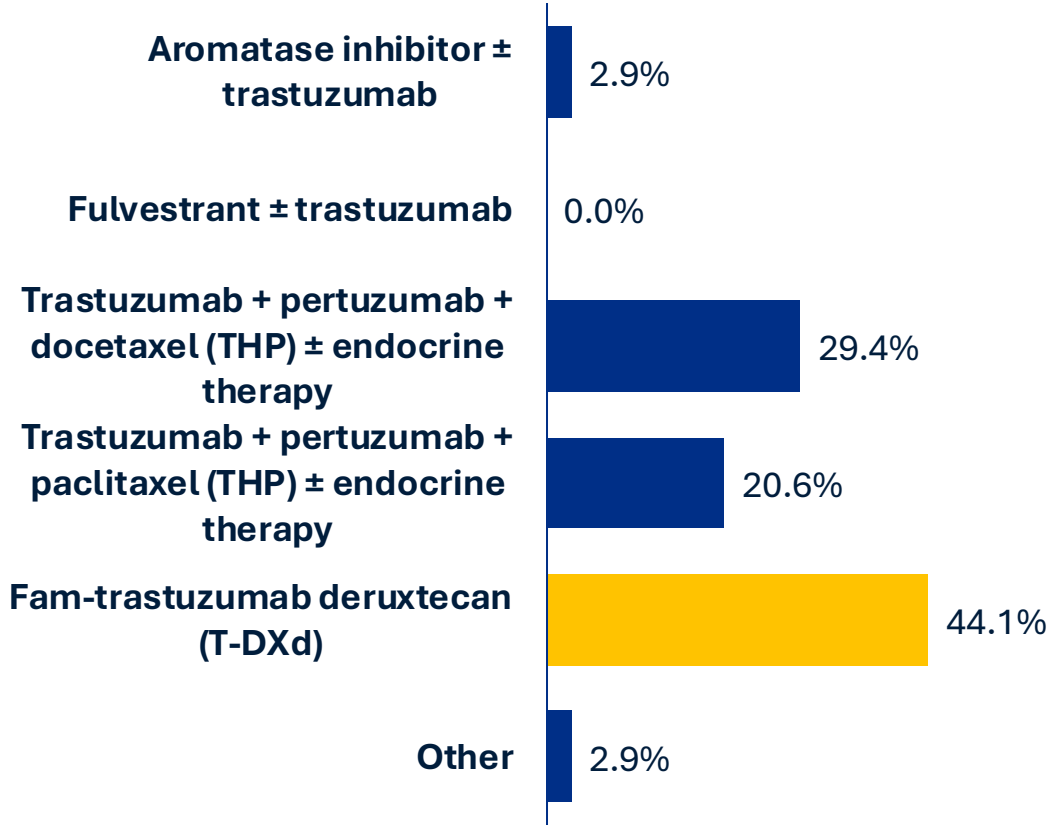
ARS Results from HCP Participants

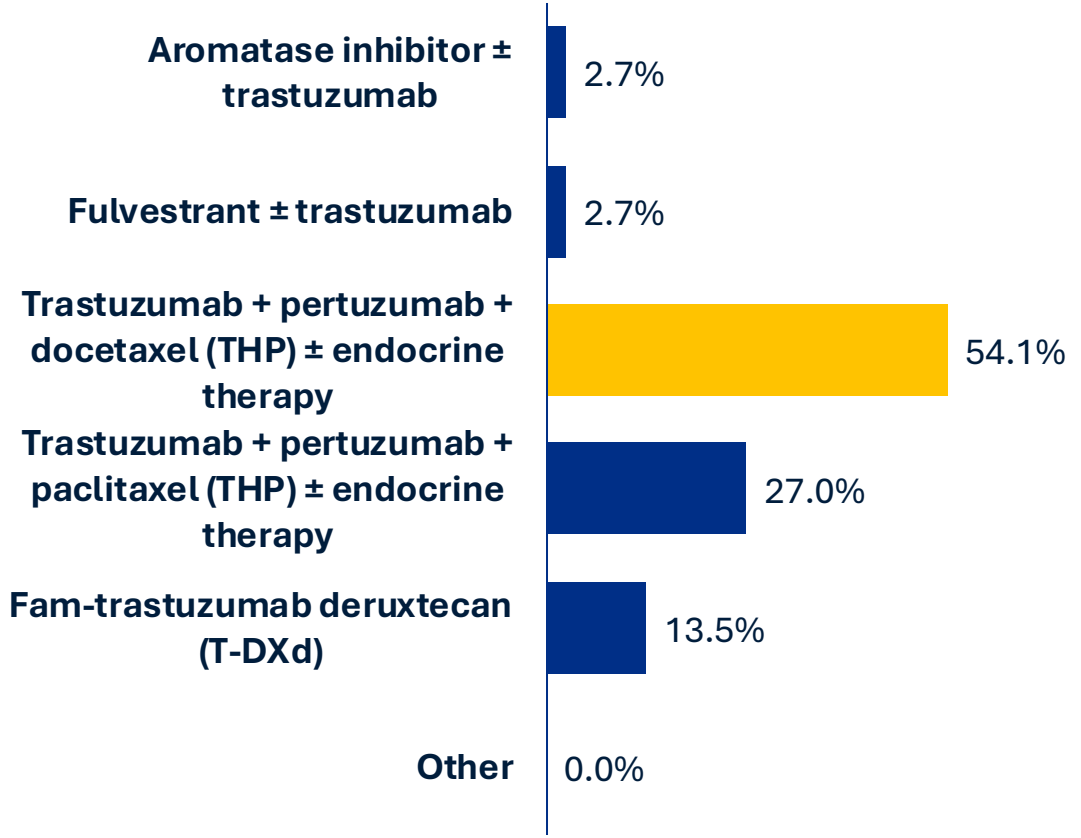
What is your 1L metastatic treatment recommendation for HR+, HER2+ mBC with >12 months to progression after neoadjuvant TC-HP, then T-DM1?



Answered: 34

ARS Results from HCP Participants

Would your frontline treatment recommendation change if HR+, HER2+ *de novo* metastatic disease?



Answered: 37

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2025
Invasive Breast Cancer

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

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)

***m*-- Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+)**

***n*-- T-DXd may be considered in the first-line setting as an option for select patients (i.e., rapid progression within 6 mo of neoadjuvant or adjuvant therapy [12 mo for pertuzumab-containing regimens])…**

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KEY DATA

CLEOPATRA: Phase 3 Double-blind Pertuzumab +/ Placebo + Trastuzumab + Docetaxel for 1st-line HER2+ mBC

Results led to what has been SOC until 2025 for most patients

- HER2+ metastatic breast cancer
- Centrally confirmed
- No prior chemotherapy or biological treatment for metastatic disease
- ECOG PS 0 – 1

(N = 808)

Stratified by geographical region (Asia, Europe, North America, or South America) and previous treatment (previous adjuvant or neoadjuvant chemotherapy vs none)

Placebo + trastuzumab + docetaxel (n=406)

Pertuzumab + Trastuzumab + docetaxel (n=402)

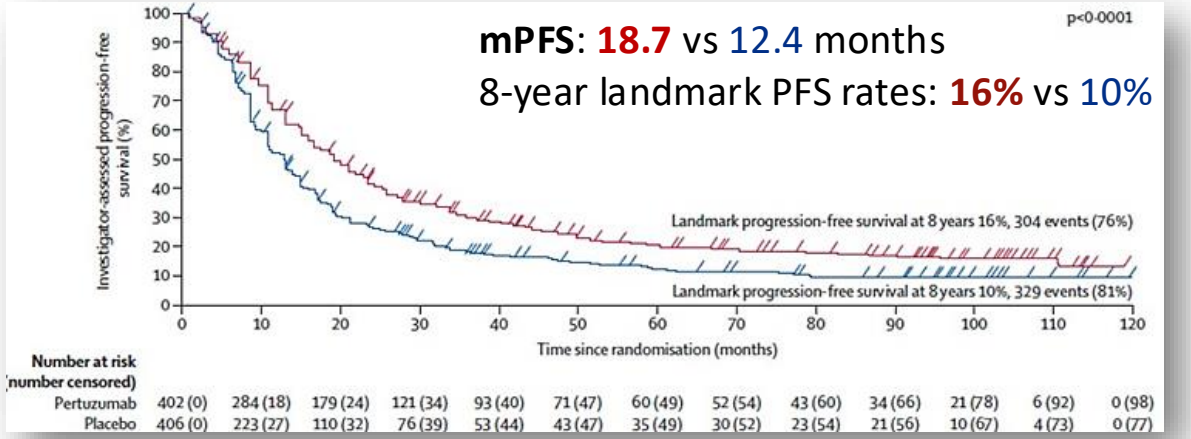
Until disease progression

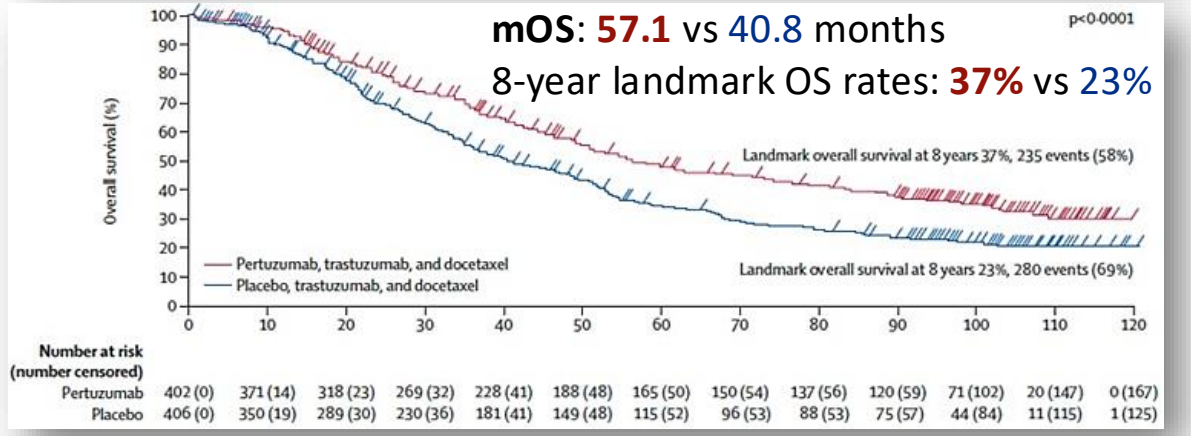
Note: 50 patients crossed over to pertuzumab arm

Pertuzumab or placebo at a loading dose of 840 mg, and 420 mg thereafter; trastuzumab at 8 mg/kg loading dose and 6 mg/kg thereafter; and docetaxel at 75 mg/m2, escalating to 100 mg/m2 if tolerated.

1ary endpoint: PFS by BICR

2ary endpoints: OS, PFS (by inv), DoR, safety





Clinical cutoff for this analysis was Nov 23, 2018

Median f/u: 99·9 mo in the pertuzumab group (IQR 92·9–106·4) and 98·7 mo (90·9–105·7) in the placebo group

Lancet Oncol. 2020; 21, 4: 519-530

mPFS data: HR+ HER2+ 1L mBC Studies

Data are before DESTINY-Breast09 release in 2025

Standard of Care THP: 18.7 mo

Lancet Oncol. 2020; 21, 4: 519-530 (CLEOPATRA)

AI + Trastuzumab: 15.8 mo

J Clin Oncol . 2018 Oct 1;36(28):2826-2835 (PERTAIN)

Endocrine therapy alone: 8.2 mo

Bull Cancer. 2012 Feb 1;99(2):E18-25.

Chemotherapy + Trastuzumab: 7.4 mo

N Engl J Med. 2001 Mar 15;344(11):783-92

Chemotherapy alone: 6.9 mo

ESMO Open 2024, vol 9, issue 9

T-DXd; *22.4 mo*

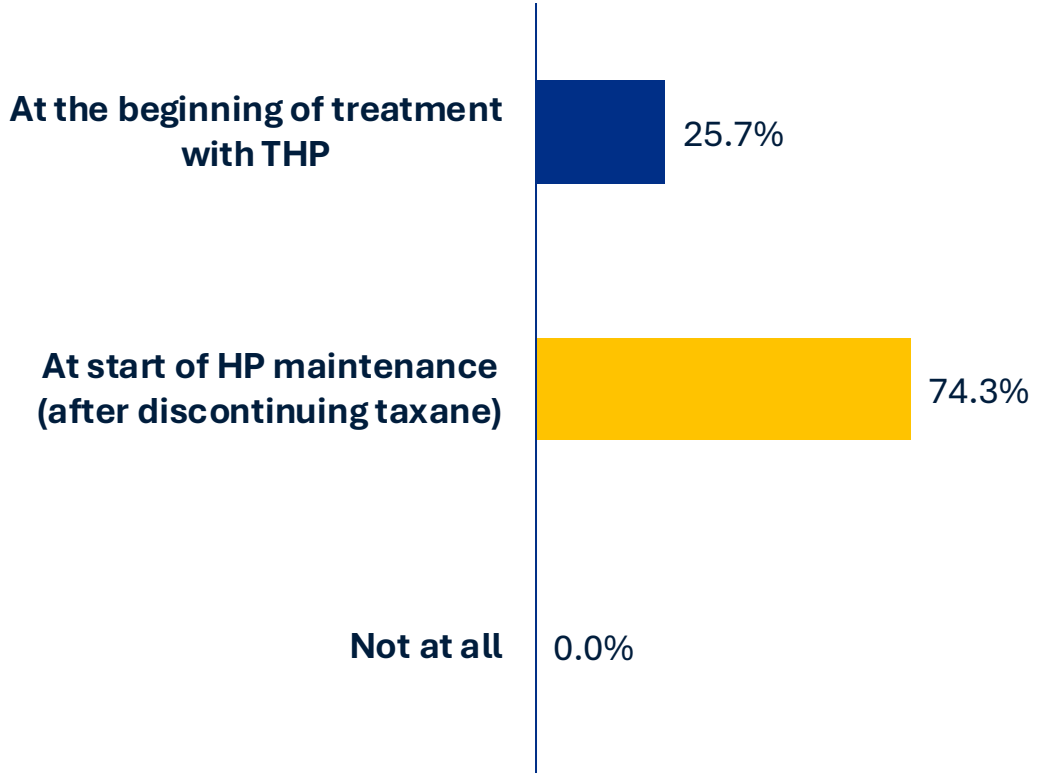
(for subset who developed disease recurrence during or within six mo of completing adjuvant therapy)

Nat Med 2024, 30, 2208-2215 (DESTINY-Breast03);

Note: eligibility is not the same in the different trials, so cross-study comparisons have caveats

ARS Results from HCP Participants

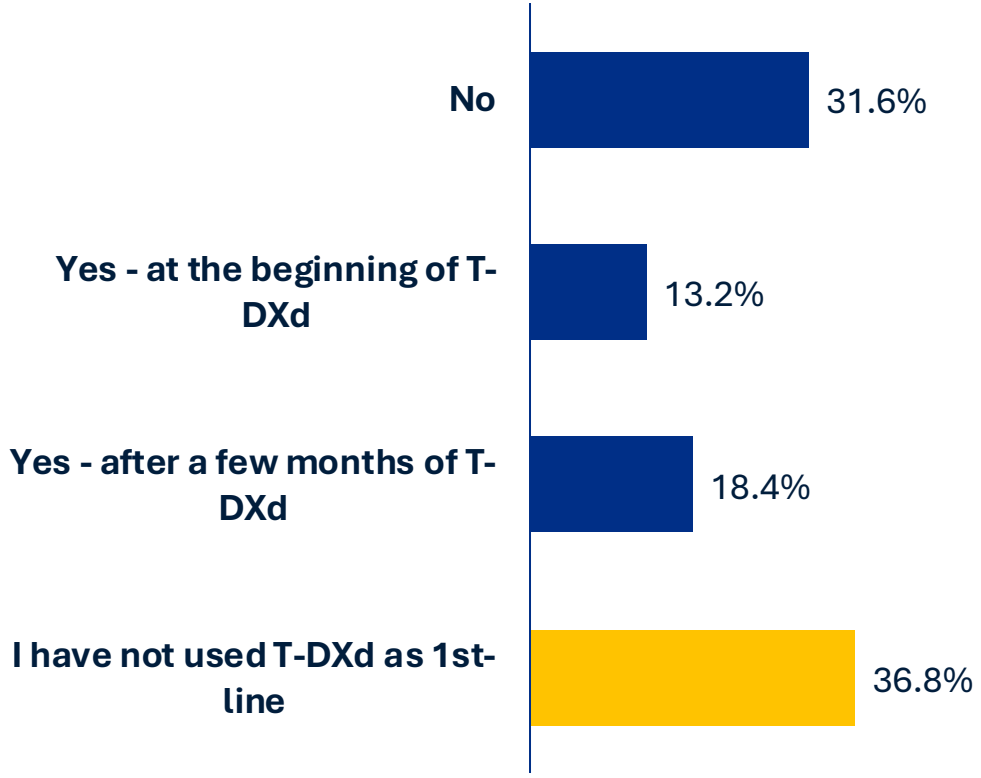
At what point do you add endocrine therapy to 1L treatment with THP for HR+, HER2+ mBC?



Answered: 35

ARS Results from HCP Participants

Have you added endocrine therapy to T-DXd if used as 1st-line for HR+ HER2+ MBC?



Answered: 38

KEY DATA: SABCS 2024

AFT-38 PATINA: Phase 3 Open Label Palbociclib with anti-HER2 therapy plus endocrine therapy in patients after induction therapy with HR+, HER2+ mBC

- Historically confirmed HR+ HER2+ mBC
- No prior treatment in the advanced setting beyond induction
- 6-8 cycles of treatment including trastuzumab with or without pertuzumab and taxane/vinorelbine
- Completion of induction chemotherapy and no evidence of disease progression (CR, PR, or SD)

(N = 518)

Stratified by pertuzumab (yes or no; non-pertuzumab limited to up to 20% of the population); prior anti-HER2 therapy in the neoadjuvant setting (yes vs no, including de novo); response to induction therapy (CR or PR vs SD); type of ET (fulvestrant vs AI)

R
1:1

Not currently FDA approved for HR+, HER2+ mBC

Palbociclib
+
Trastuzumab ± pertuzumab + endocrine therapy
(n=261)

Trastuzumab ± pertuzumab + endocrine therapy
(n=257)

Until progressive disease or toxicity

1ary endpoint: Investigator assessed PFS
2ary endpoint: OS, ORR, Safety

Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor (AI) or fulvestrant.

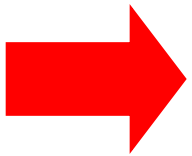
KEY DATA: SABCS 2024

AFT-38 PATINA: Phase 3 Open Label Palbociclib with anti-HER2 therapy plus endocrine therapy in patients after induction therapy with HR+, HER2+ mBC

Baseline Characteristics

	Palbociclib + anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Age, Median (Range)	53.3 (43.6 – 60.4)	53.0 (45.1 – 62.8)
Number of cycles of induction therapy		
• Median (range)	6 (4 – 8)	6 (4 – 8)
Pertuzumab use		
• Yes	253 (96.9%)	251 (97.7%)
• No	8 (3.1%)	6 (2.3%)
Type of Endocrine therapy		
• Aromatase inhibitor	237 (90.8%)	234 (91.1%)
• Fulvestrant	24 (9.2%)	23 (8.9%)
Prior anti-HER2 in (neo)adjuvant setting		
• Yes	190 (72.8%)	182 (70.8%)
• No	71 (27.2%)	75 (29.2%)
Best response to induction therapy by investigator assessment		
• CR or PR	179 (68.6%)	176 (68.5%)
• SD	82 (31.4%)	81 (31.5%)

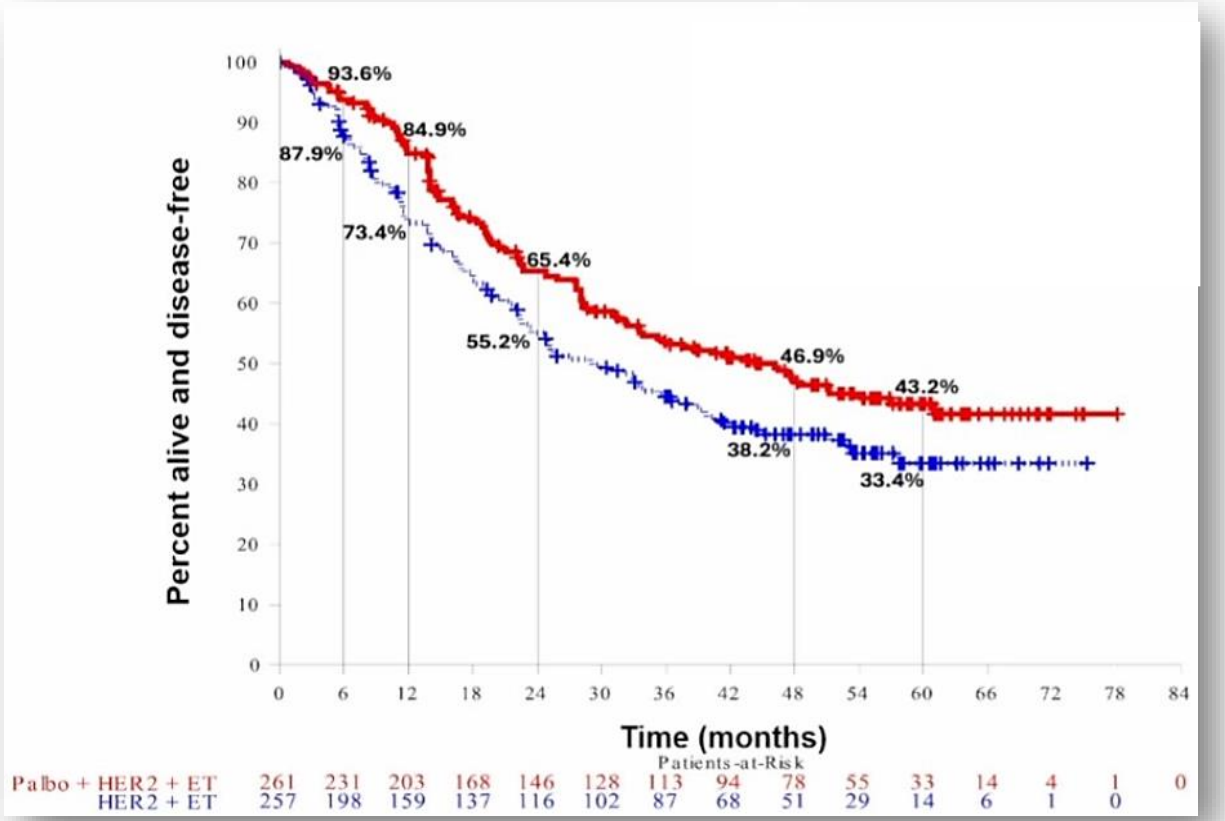
Reminder: *if a patient did not achieve at least stable disease in the first 6 months of therapy, the pt was not eligible for this trial*



KEY DATA: SABCS 2024

AFT-38 PATINA: Phase 3 Open Label Palbociclib with anti-HER2 therapy plus endocrine therapy in patients after induction therapy with HR+, HER2+ mBC

Primary Endpoint: PFS (Investigator-assessed)



Secondary Endpoints OS

Interim analysis	Palbociclib + anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Median OS, Months (95% CI)	**NE** (71.6 – NE)	**77** (72.0 – NE)
3-yr OS, % (95% CI)	**87.0%** (82.8 – 91.2)	84.7 % (80.0 – 89.3)
5-yr OS, % (95% CI)	**74.3%** (67.7 – 80.9)	69.8% (62.4 – 77.2)
HR (95% CI)	**0.86** (0.60 – 1.24)	
Median PFS, Months (95% CI)	**44.3** (32.4 – 60.9) **Δ 15.2 months**	**29.1** (23.3 – 38.6)
HR (95% CI)	**0.74** (0.58 – 0.94); *P* = 0.0074	

AFT-38 PATINA: Phase 3 Open Label Palbociclib with anti-HER2 therapy plus endocrine therapy in patients after induction therapy with HR+, HER2+ mBC

Safety Data

	Palbociclib + anti-HER2 + ET (n=261)			Anti-HER2 + ET (n=257)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9%)	165 (63.2%)	12 (4.6%)	10 (4.0%)	11 (4.4%)	0 (0.0%)
White blood cell count decreased	30 (11.5%)	30 (11.5%)	1 (0.4%)	2 (0.8%)	0 (0.0%)	0 (0.0%)
Fatigue	60 (22.9%)	14 (5.4%)	0 (0.0%)	32 (12.9%)	0 (0.0%)	0 (0.0%)
Stomatitis	45 (17.2%)	11 (4.2%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)
Diarrhea	69 (26.4%)	29 (11.1%)	0 (0.0%)	26 (10.5%)	4 (1.6%)	0 (0.0%)
Upper respiratory tract infection	30 (11.5%)	1 (0.4%)	0 (0.0%)	16 (6.5%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	26 (10.0%)	2 (0.8%)	0 (0.0%)	19 (7.7%)	1 (0.4%)	0 (0.0%)
Arthralgia	23 (8.8%)	4 (1.5%)	0 (0.0%)	44 (17.7%)	3 (1.2%)	0 (0.0%)
Ejection fraction decreased	22 (8.4%)	1 (0.4%)	0 (0.0%)	21 (8.5%)	8 (3.2%)	0 (0.0%)
Cardiac heart failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	0 (0.0%)

Adverse events were assessed per Common Terminology Criteria for Adverse Events, version 4.0 regardless of treatment attribution. Stomatitis, mouth ulceration, mucosal inflammation, and mucositis were assessed as medical concepts using grouped terms. Fatigue and asthenia were assessed as medical concepts using grouped terms. Cardiac safety data were also included in the table above. AE = adverse events.

KEY DATA: ESMO 2025

DESTINY-Breast09: T-DXd ± Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ a/mBC

T-DXd + Pertuzumab: not yet FDA approved

Study Design: Phase 3

- HER2+* (IHC3+ or ISH+) advanced or mBC
- No previous chemo or HER2-targeted therapy for advanced or metastatic disease
- Previous chemo/HER2-targeted therapy allowed in neoadjuvant setting if >6 mo from metastatic disease diagnosis
- One prior line of ET for mBC permitted
- Asymptomatic/inactive brain mets allowed
- ECOG PS 0/1

(N = 1157)

R 1:1:1

Continued Until PD or death

T-DXd 5.4 mg/kg q3w
(Blinded until final PFS analysis)
(n=387)

T-DXd 5.4 mg/kg q3w + **Pertuzumab**
(n=383)

Taxane + Pertuzumab + Trastuzumab (TCP)†
(n=387)

Endpoints

Primary
- PFS (BICR)

Key secondary
- OS

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

Stratification factors
- De-novo (~52%) vs recurrent a/mBC
- HR+ (~54%) or HR−
- *PIK3CA*m detected (~31%) vs not detected

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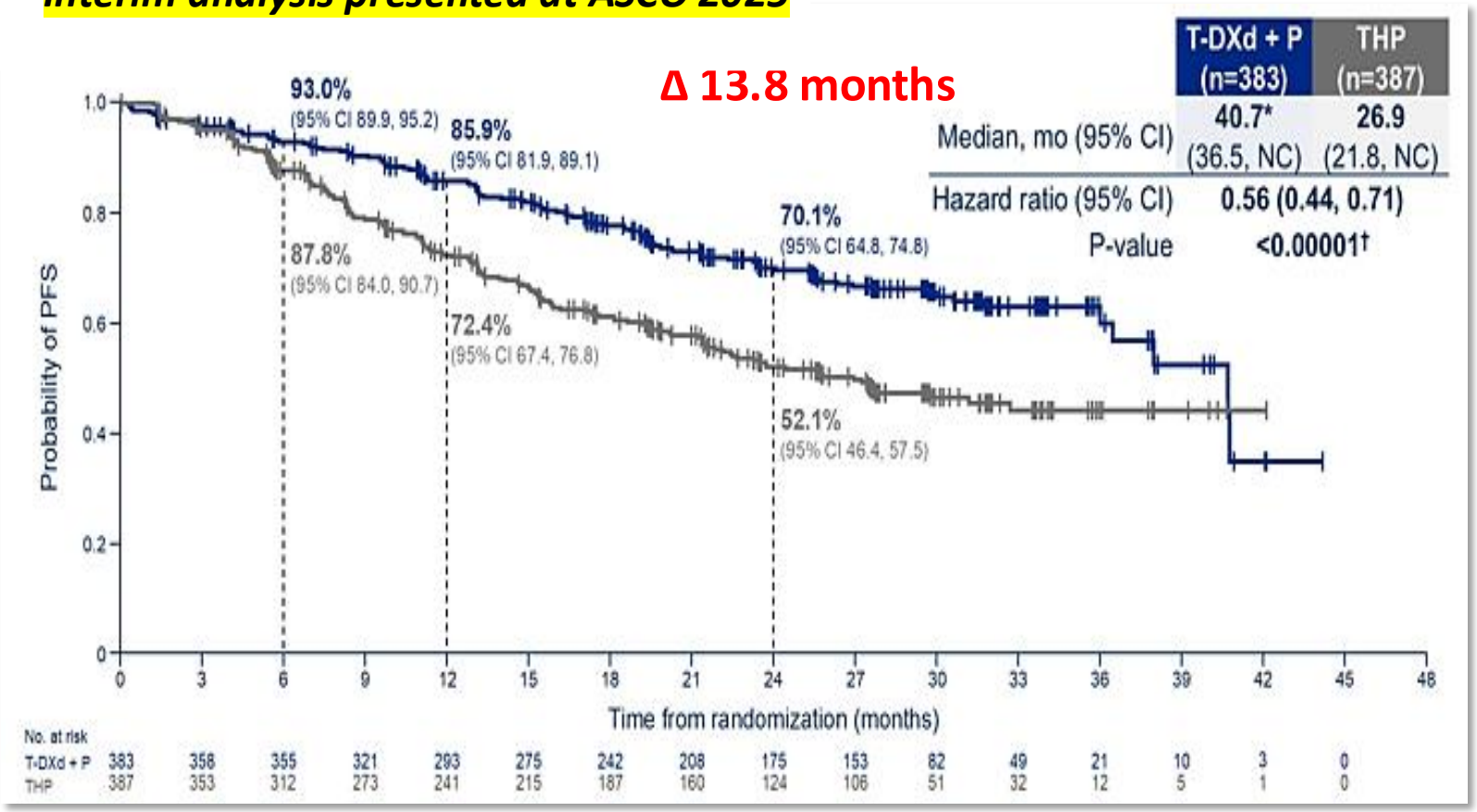
ESMO 2025 LBA18

KEY DATA

DESTINY-Breast09: 1L T-DXd ± Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ a/mBC, **Primary Endpoint**: **PFS by BICR**

Interim analysis presented at ASCO 2025



Median PFS by prior treatment status		
	T-DXd + P	**THP**
de novo	**NC** 95% CI: 36.5, NC	**31.2 mo** 95% CI: 23.5, NC
recurrent	**38.0 mo** 95% CI: 26.9, NC	**22.5 mo** 95% CI: 18.1, NC

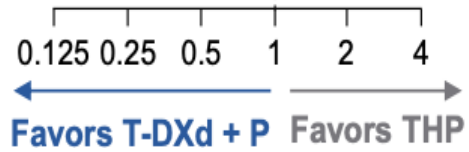
NC, not calculable

ASCO 2025 LBA1008; ESMO 2025 LBA18

KEY DATA: ESMO 2025

DESTINY-Breast09: 1L T-DXd ± Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ a/mBC, ***PFS2 by Subgroup**

	No. of events / no. of patients		mPFS2, mo (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	38/200	59/200	NC	37.4 (36.1, NC)	0.55 (0.36, 0.83)
Recurrent	41/183	56/187	NC	36.5 (30.2, NC)	0.66 (0.44, 0.99)
HR status					
Positive	38/207	62/209	NC	NC (33.2, NC)	0.54 (0.36, 0.81)
Negative	41/176	53/178	NC (39.6, NC)	36.5 (33.1, NC)	0.67 (0.44, 1.01)
***PIK3CA*m status**					
Detected	29/116	44/121	NC	33.2 (24.2, NC)	0.57 (0.35, 0.91)
Not detected	49/266*	71/266	NC (39.6, NC)	37.4 (36.1, NC)	0.61 (0.42, 0.87)

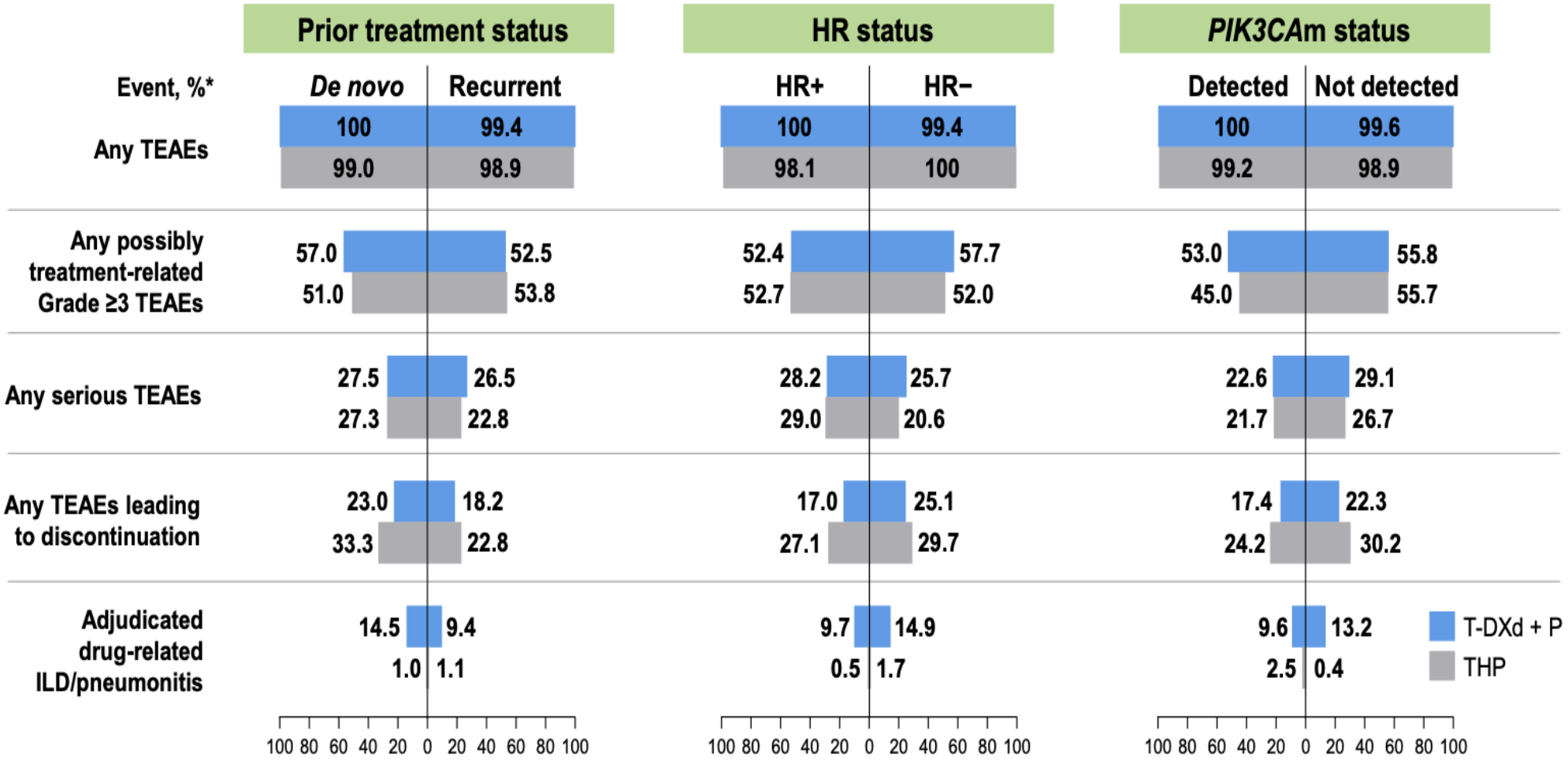


Note: Size of circle is proportional to the number of events

*PFS2 was defined by investigators according to local standard clinical practice as the time from randomization to second progression (earliest progression event following first subsequent therapy) or death

KEY DATA: ASCO 2025

DESTINY-Breast09: 1L T-DXd ± Pertuzumab vs Pertuzumab + Trastuzumab + Taxane in HER2+ a/mBC, **Safety**



Median total treatment duration:

- **T-DXd + P: 21.7 mo** (range .3 to 44.5)
- **THP: 16.9 mo** (range 0.7 to 41.7)

Median treatment duration for taxanes:

- **Docetaxel: 5.5 mo** (range .7 to 37.4); median **8** cycles
- **Paclitaxel: 4.4 mo** (range 0.2 to 3.7); median **6** cycles

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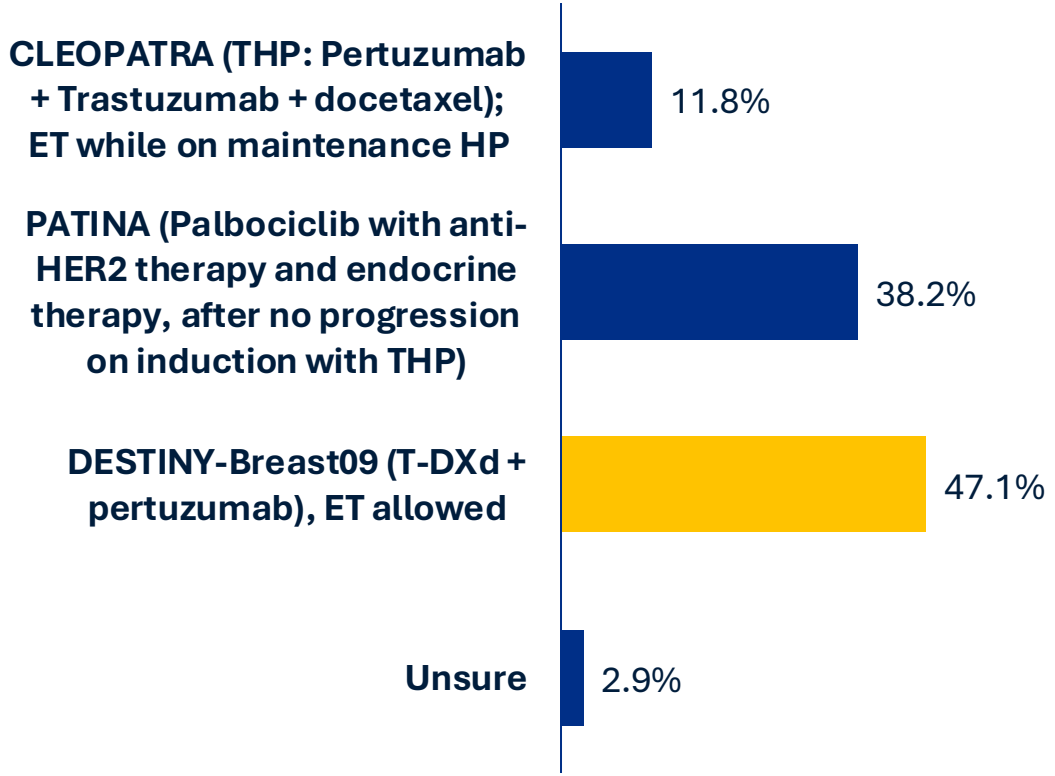
ESMO 2025 LBA18

ARS Results from HCP Participants

What would be your preference for 1L HR+, HER2+ mBC if DESTINY-Breast09 and/or PATINA are approved?



Answered: 34

CLEOPATRA THP		PATINA TH±P → Palbo + anti-HER2 + ET		DESTINY-Breast09 T-DXd + Pertuzumab	
Current Approved SoC		***Not yet FDA approved***			
• **No prior chemotherapy or biological treatment for metastatic disease**		• **6-8 cycles of treatment including trastuzumab with or without pertuzumab and taxane/vinorelbine** • **Completion of induction chemotherapy and no evidence of disease progression (CR, PR, or SD)**		• **No previous chemo or HER2-targeted therapy for advanced or metastatic disease** • **Previous chemo/HER2-targeted therapy allowed in neoadjuvant setting if >6 mo from metastatic disease diagnosis** • **One prior line of ET for mBC permitted**	
Pertuzumab + trastuzumab + docetaxel (n=402)	Placebo + trastuzumab + docetaxel (n=406)	**Palbociclib** + trastuzumab ± pertuzumab + endocrine therapy (n=261)	Placebo + trastuzumab ± pertuzumab + endocrine therapy (n=261)	**T-DXd** + pertuzumab (n=383)	Taxane + pertuzumab + trastuzumab (TCP)† (n=387)
Medium follow-up: 99.9 months	98.7 months	Medium follow-up: **52 months**		Medium follow-up: **29.2 months**	
mPFS: **18.7**	12.4 months	**mPFS: 44.3**	29.1 months	**mPFS: 40.7**	26.9 months
8-year landmark PFS rates: **16%** vs 10%		**HR: 0.74** (0.58 – 0.94); P = 0.0074		**HR: 0.56** (0.44 – 0.71); P = 0.00001	
mOS: **57.1**	40.8 months	*Not evaluable* (*OS immature*)	77 months	*Not calculable*	*Not calculable*
8-year landmark OS rate: **37%** vs 23%		**3-year OS rate: 87.0%** vs 84.7 %		HR 0.84 (*OS immature*)	

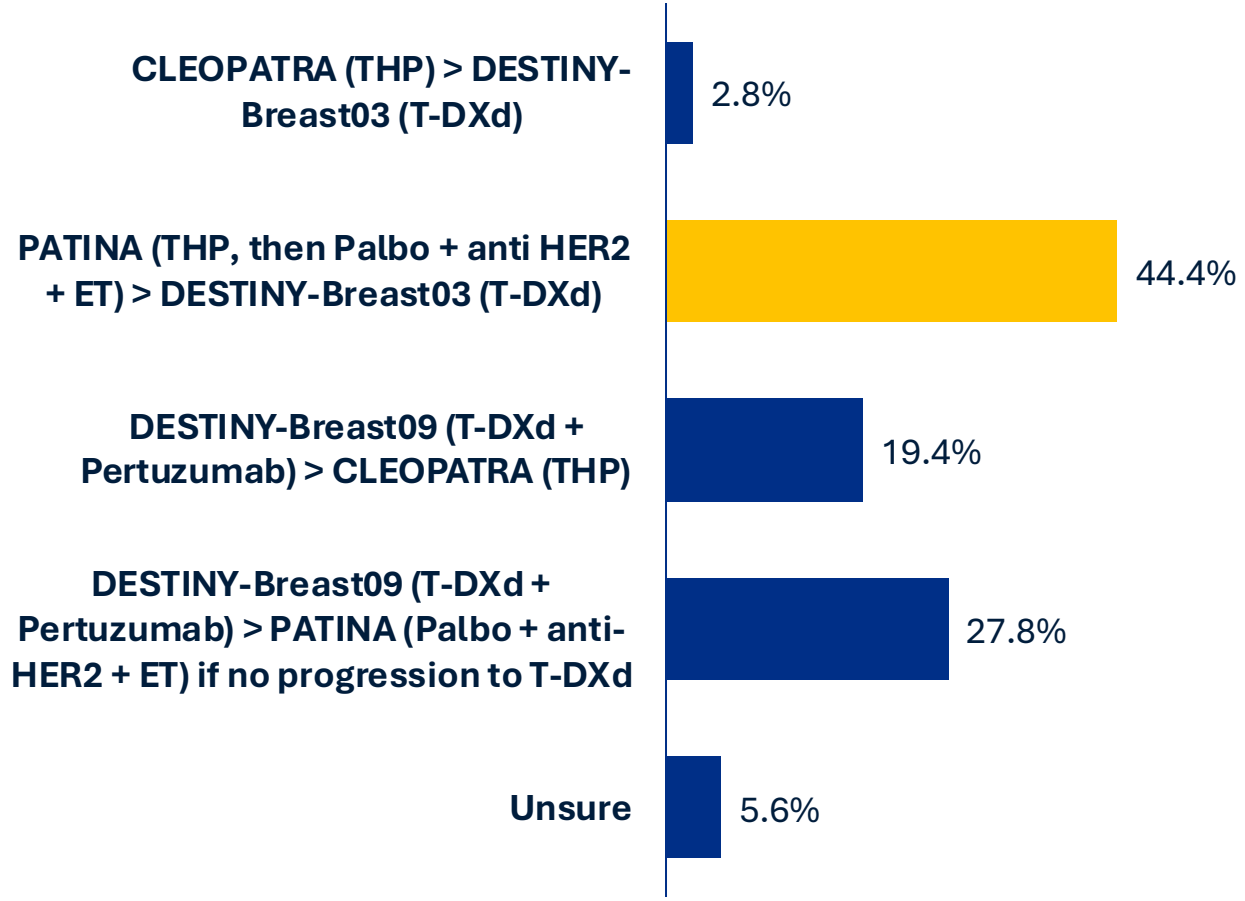
N Engl J Med. 2012 Jan 12;366(2):109-19.

SABCS 2024 Abstract GS2-12

ESMO 2025 LBA18

ARS Results from HCP Participants

How do you plan to manage patients eligible for Rx for 1st-line HR+ HER2+ MBC if the DB-09 and PATINA regimens are approved by the FDA?



Answered: 36

Key Takeaways

HER2-positive Breast Cancer

Patient Case: 1st line mBC

- *Current standard of care (CLEOPATRA) with long term follow up has been impactful for many years but still room for improvement*
    - *PFS: 18.7 months; OS: 57.1 months*
    - 8-year landmark PFS rates: **16%;** 8-year landmark OS rates: **37%**

- *Patina and Destiny-09 yielded mPFS results that are better than the Cleopatra regime of THP without ET (different patient populations)*
    - *PATINA: palbo + trastuzumab + ET after completion of induction chemotherapy and no evidence of disease progression (CR, PR, or SD)*
        - *PFS: 44.3 months; OS: Not evaluable (interim analysis)*
    - *DB09: one prior line of ET for mBC permitted; benefit regardless of PIK3CA mutation, HR status or de novo vs recurrent disease. PFS2 also better for participants who started on T-DXd*
        - *PFS: 40.7 months; OS: Not evaluable (interim analysis:* ~16% maturity)