Advances in the Treatment of Breast Cancer: Selected Topics

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Southeastern Multidisciplinary Approaches to Cancer Symposium

Most Impactful Discoveries in Breast Cancer Care and How We Continue to Move the Needle for Our Patients

(selected topics)

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Disclosures

- Grant/Research Support to UCSF from AstraZeneca, Ambryx, Daiichi Sankyo, Eli Lilly, F.Hoffman-LaRoche/Genentech, Gilead Sciences, Merck & Co., Novartis, Pfizer, Stemline Therapeutics
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- Consultant for BrBioNTech, Bristol Myers Squibb, Helsinn, and Nap

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research studies. A direct patient care component is part of these studies. Almost all included studies included a broad geographic international population with racial and ethnic diversity However, implicit bias exists with smaller enrollment from the US and low representation of US minority populations Access to treatment is impacted by geography, proximity to specialized cancer care, and insurance coverage

The Bigger Picture

- Treatment progress is reflected in improved survival
- The pace of new drug approvals is accelerating!
- AI to aid in interpretation of imaging and pathology; treatment decision making in complex settings

44% decline in U.S. decline in U.S. breast cancer death rate since its 1989 peak, avoiding an estimated 546,000 deaths

At least 6 major FDA approvals in the past year covering endocrine therapy, ADCs, and HER2+ early disease

70% of breast cancers are hormone receptor+ / HER2- — the focus of new oral SERDs and novel targeted agents

Drug Approvals Since January 2025 for Breast Cancer and More

- ADCs
  - T-DXd
  - Datopotomab DXd
  - Sacituzumab govitecan
- Oral SERDS in metastatic and early stage disease
- New targeted agents for HR+ disease
  - Gedatolisib
- Advances in biomarkers
  - Bringing ctDNA into the clinic

Key Advances and New Directions in Breast Cancer Treatment

- **Treatment**
  - Recognizing the importance of neoadjuvant therapy
    - Allows escalation and de-escalation based on response to therapy
    - Refining post-neoadjuvant therapy
  - Matching treatment to biology
    - Optimizing chemotherapy, use of immunotherapy, optimal and new endocrine therapy, combinations with targeted therapy
  - Understanding optimal sequencing in the treatment of metastatic disease
    - Improving symptom management
      - Prophylaxis and proactive monitoring and action
- **Biomarkers**
  - Rapid NGS on tissue and ctDNA to direct targeted therapies
    - Which test, when and how to employ remain major questions
- **Many questions remain!**

Major Advances in the Last Year!

- **HER2+ Disease**
  - ADCs > than 1st generation ADC or chemo + HER2 targeted Rx in metastatic disease
    - Maintenance HER2 therapy combined with targeted agents therapy prolongs response
    - Activity in treating, ?preventing brain metastases
  - HER2 ADC > chemo and 1st generation ADC for early-stage disease
  - Escalating therapy in early-stage disease
    - HER2 ADC in sequence or rescue
- **HR+ disease**
  - New endocrine therapy for early and metastatic disease; over coming acquired resistance
  - Identifying HER2 low and ultra-low as predictors of response to trastuzumab deruxtecan
  - Targeting resistance pathways – novel agents!
  - Using molecular resistance markers to drive treatment change
- **TNBC**
  - IO for treatment of early-stage and metastatic disease
  - TROP2 ADCs > chemotherapy +/- IO in metastatic disease
  - Classifying ER low as TNBC

Examples of Major Advances

Trastuzumab deruxtecan:
Efficacy across HER2 expression

Trastuzumab deruxtecan in HER2+ MBC

Destiny Breast-03

Long-term survival analysis

Median FU 41 months

Demographics

- 50% HR+
- 15% baseline brain mets
- 70% visceral disease
- 61% prior pertuzumab
- Median 2 lines of prior therapy

Anti-cancer therapies in post-trial setting:

- **T-DXd arm**: 52% received T-DM1
- **T-DM1 arm**: 32.3% received T-DXd

Updated AEs

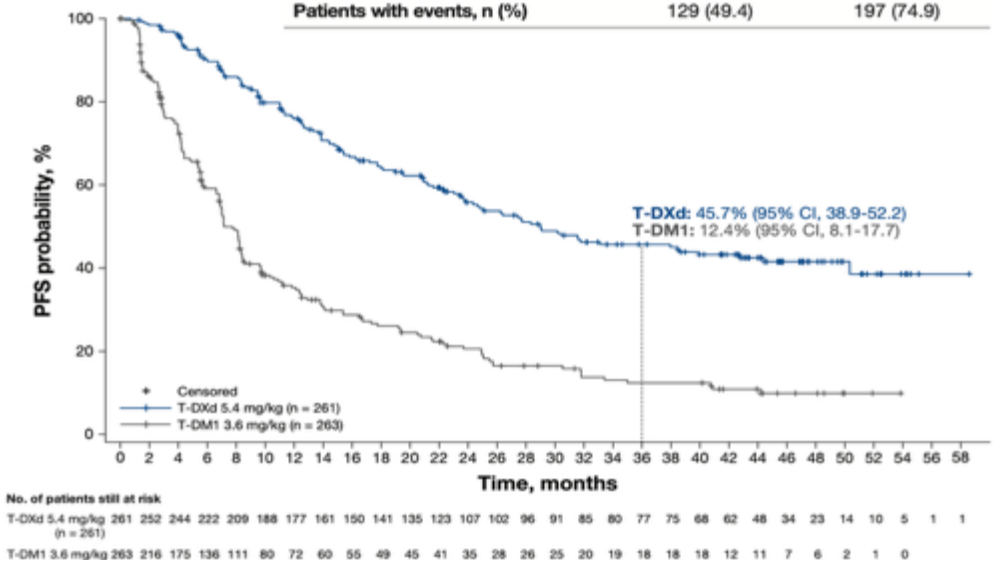
- ILD: 16.7%, no grade 4 or 5 (10% in the first 12 mo)

All grade AE

- Nausea: 77%
- Vomiting: 53%
- Alopecia 40%
- Neutropenia ≥grade 3: 16%

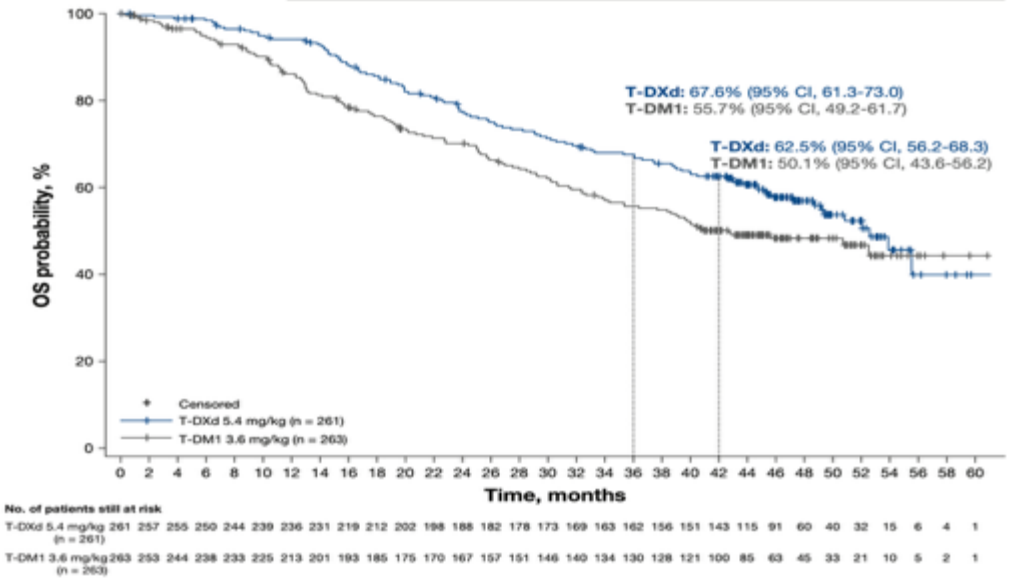
PFS by investigator assessment

	T-DXd n = 261	T-DM1 n = 263
Median (95% CI), months	29.0 (23.7-40.0)	7.2 (6.8-8.3)
HR (95% CI)	0.30 (0.24-0.38)	
Patients with events, n (%)	129 (49.4)	197 (74.9)



Overall Survival

	T-DXd n = 261	T-DM1 n = 263
Median (95% CI), months	52.6 (48.7-NE)	42.7 (35.4-NE)
HR (95% CI)	0.73 (0.56-0.94)	
Patients with events, n (%)	110 (42.1)	126 (47.9)

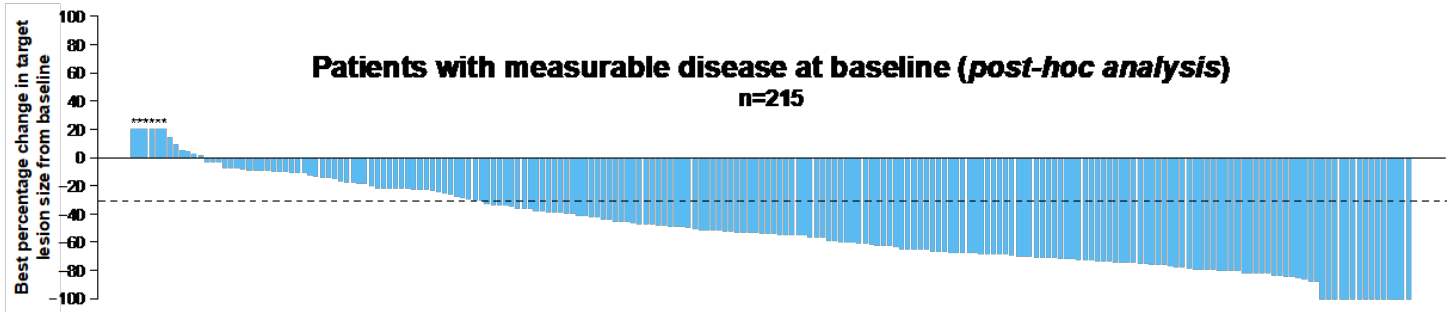


Hurvitz S et al. Lancet Oncology 2023; Hamilton et al, ASCO 2024; Cortes et al, Nature Med 2024

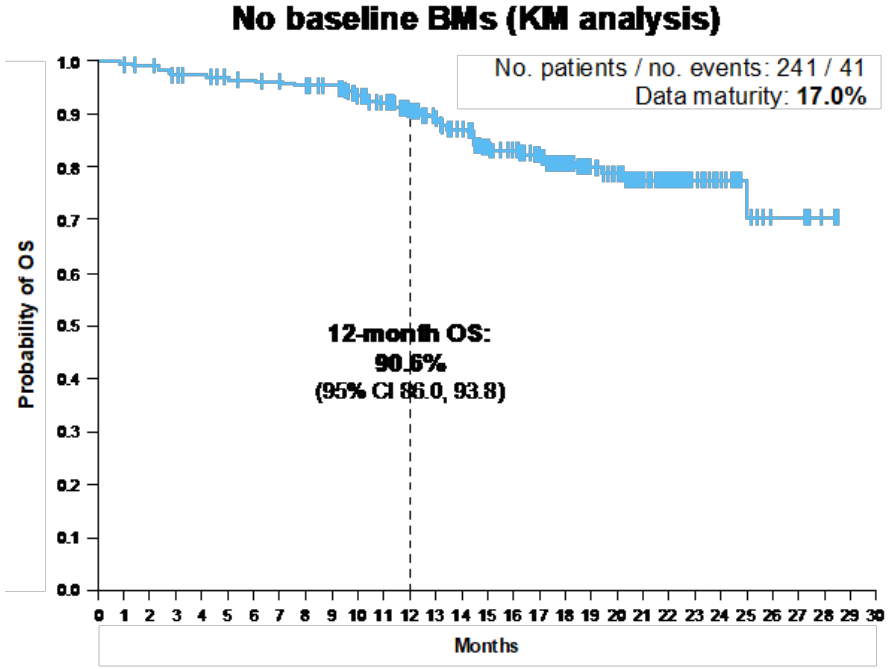
DESTINY Breast-12

No baseline BMs: ORR (primary endpoint)

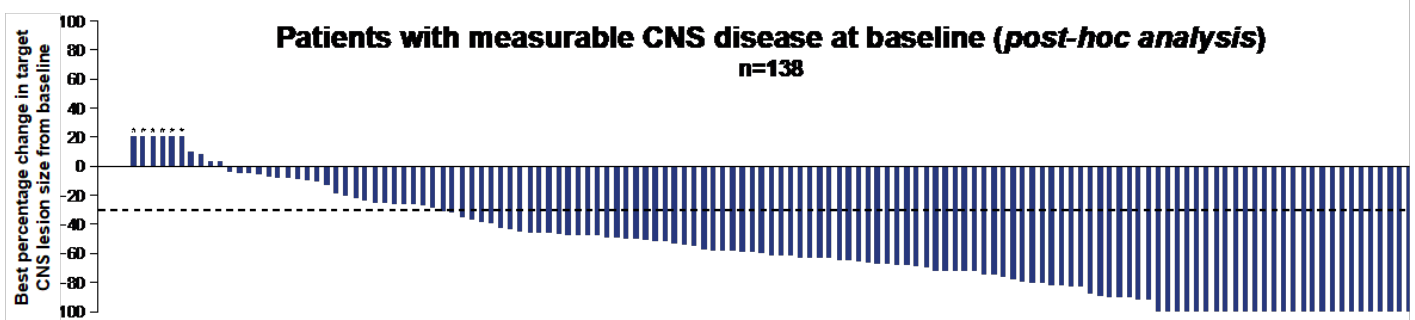
ORR is in line with previous Phase 3 T-DXd trials in this setting[1,2]



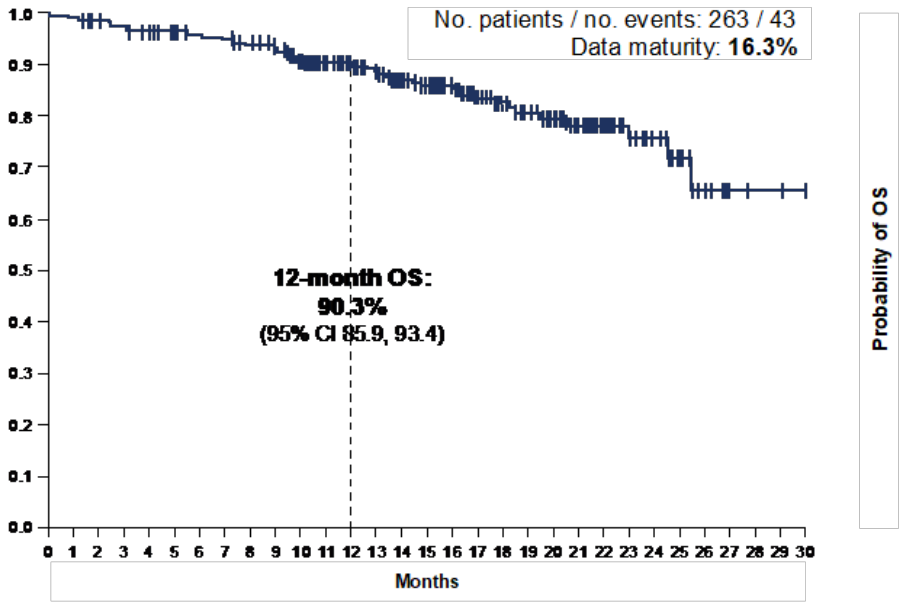
	Full analysis set Overall population (N=241)†	Measurable disease at baseline (n=215) *Post-hoc analysis*
Confirmed ORR, % (95% CI)	**62.7 (56.5, 68.8)**	**68.4 (62.2, 74.6)**
CR, n (%)	23 (9.5)	20 (9.3)
PR, n (%)	128 (53.1)‡	127 (59.1)



Baseline BMs: CNS ORR



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)

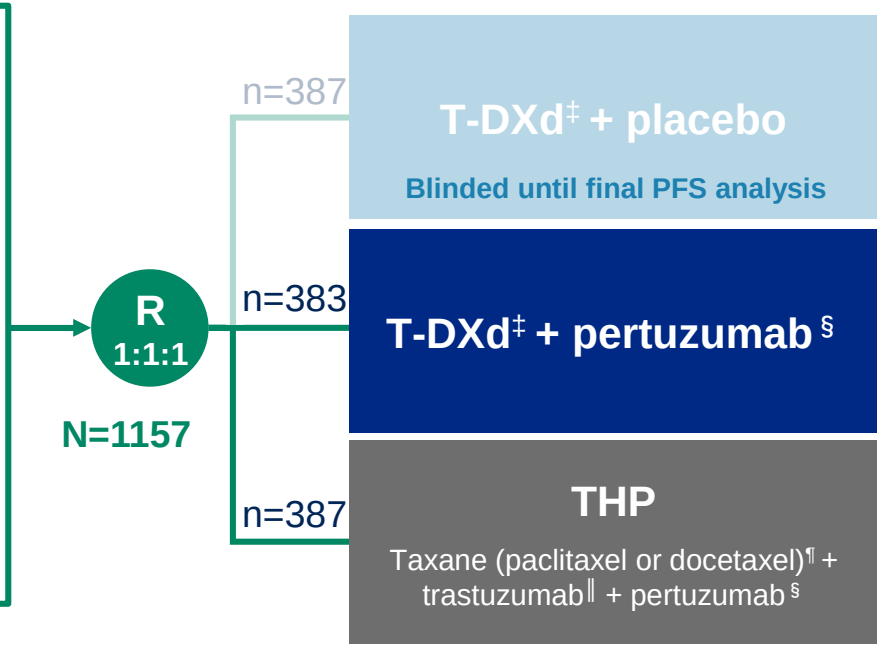


Harbeck et al, Nat Med 2024

Destiny-Breast09: Moving T-DXd to the 1st Line Setting

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

Stratification factors

- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

ET allowed after TDXd x 6 or off taxane

At DCO: 45.8% (n=174) T-DXd + P vs 33.4% (n=128) THP remained on any therapy

At the 1st planned interim analysis (DCO Feb 26, 2025), results were reported for the T-DXd + P and THP arms

Demographics

49% were treated in Asia

82% HER2 3+; 54% HR+; 30% PIK3CA mutations

52% had de novo metastatic disease, 71% visceral mets, 6% brain mets

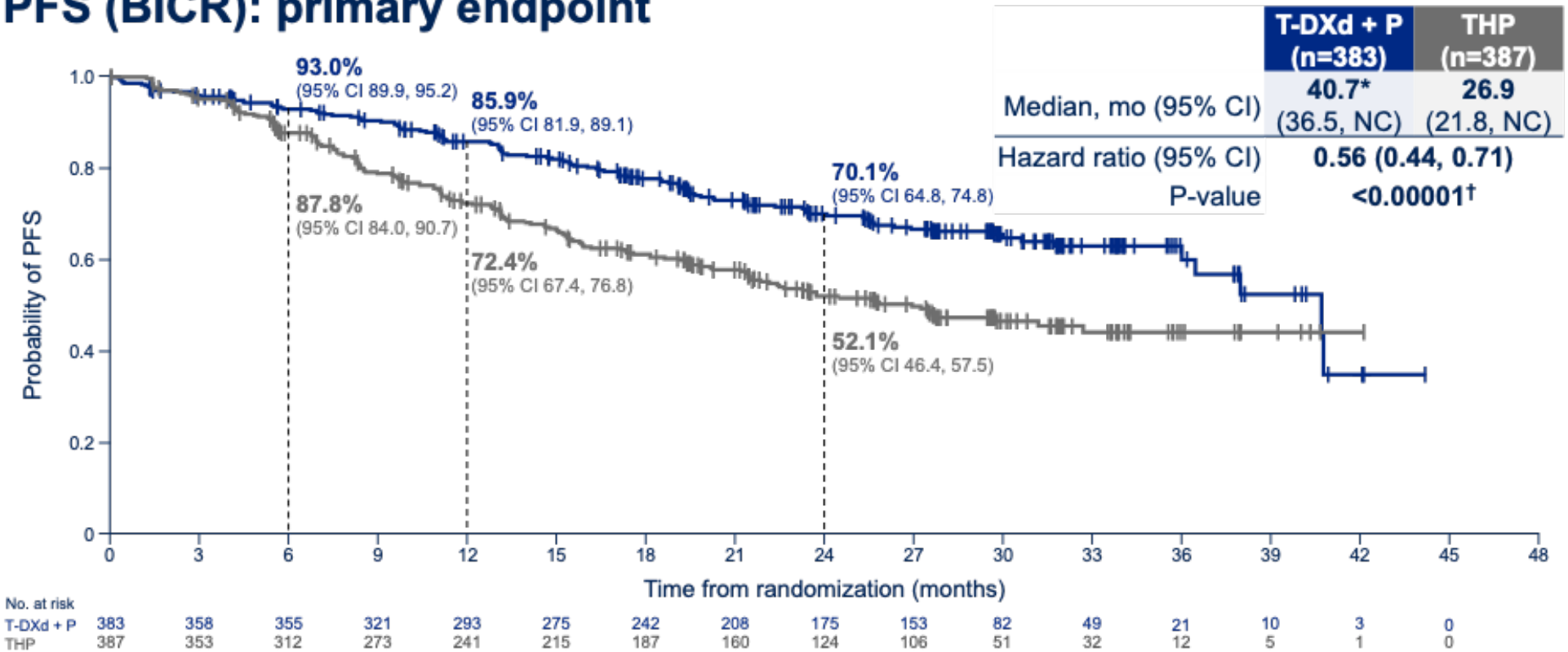
Prior therapy

Only 7% had prior pertuzumab, 1% prior T-DM1 and 28.5% prior trastuzumab

40% prior chemotherapy, 20% prior ET

Tolaney et al, NEJM 2025

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†	

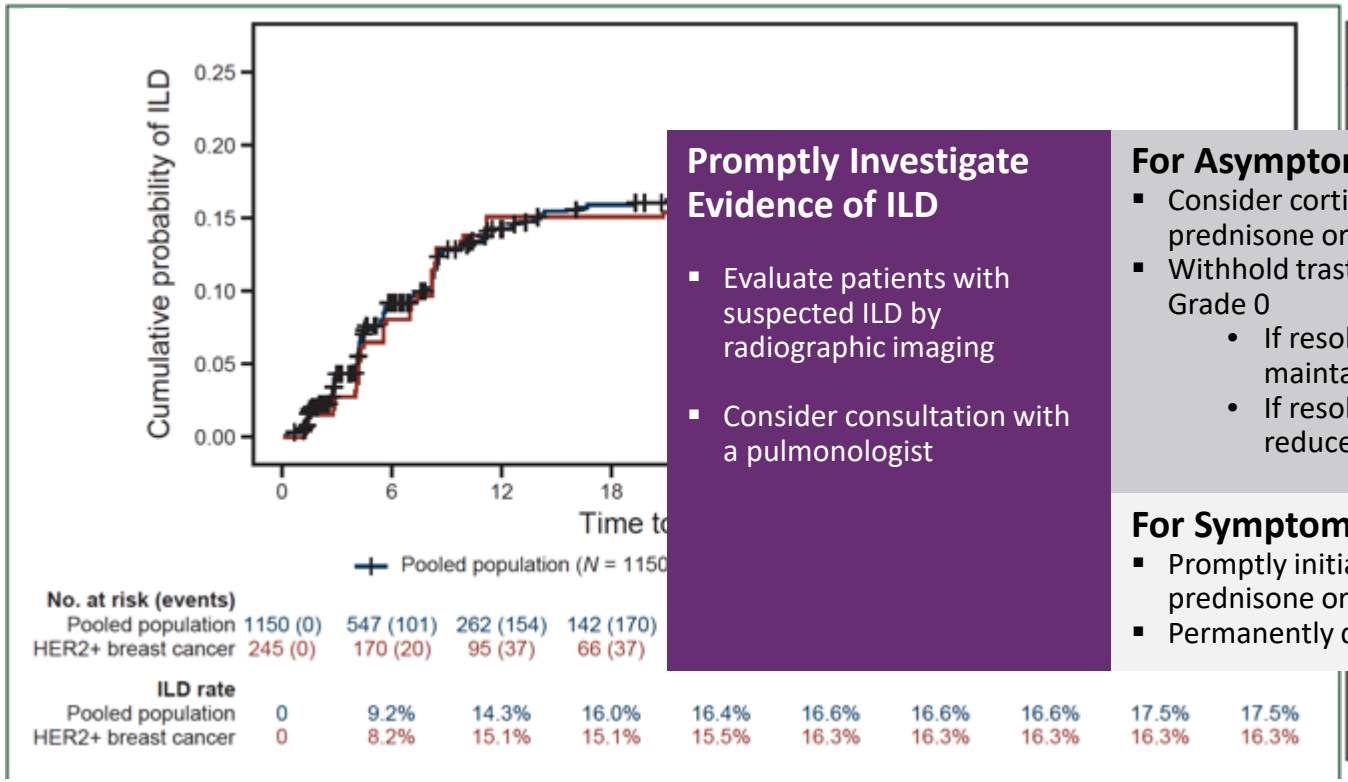
Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*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

- Consistent PFS benefit with T-DXd + P observed across stratification factors
  - Recurrent disease / prior treatment (~50% of patients in this setting)
  - HR-negative status (~50% of patients)
  - PIK3CA mutation (~30% of patients)

- Updates ESMO 2025 (Loibl et al)
  - PFS and ORR benefit seen across
    - Denovo and recurrent disease: HR 0.49 v 0.63
    - Across HR status: HR+ 0.61, HR- 0.52
    - Across mPIK3CA status: mut 0.52, wt 0.57

Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab deruxtecan Monotherapy Studies



Promptly Investigate Evidence of ILD

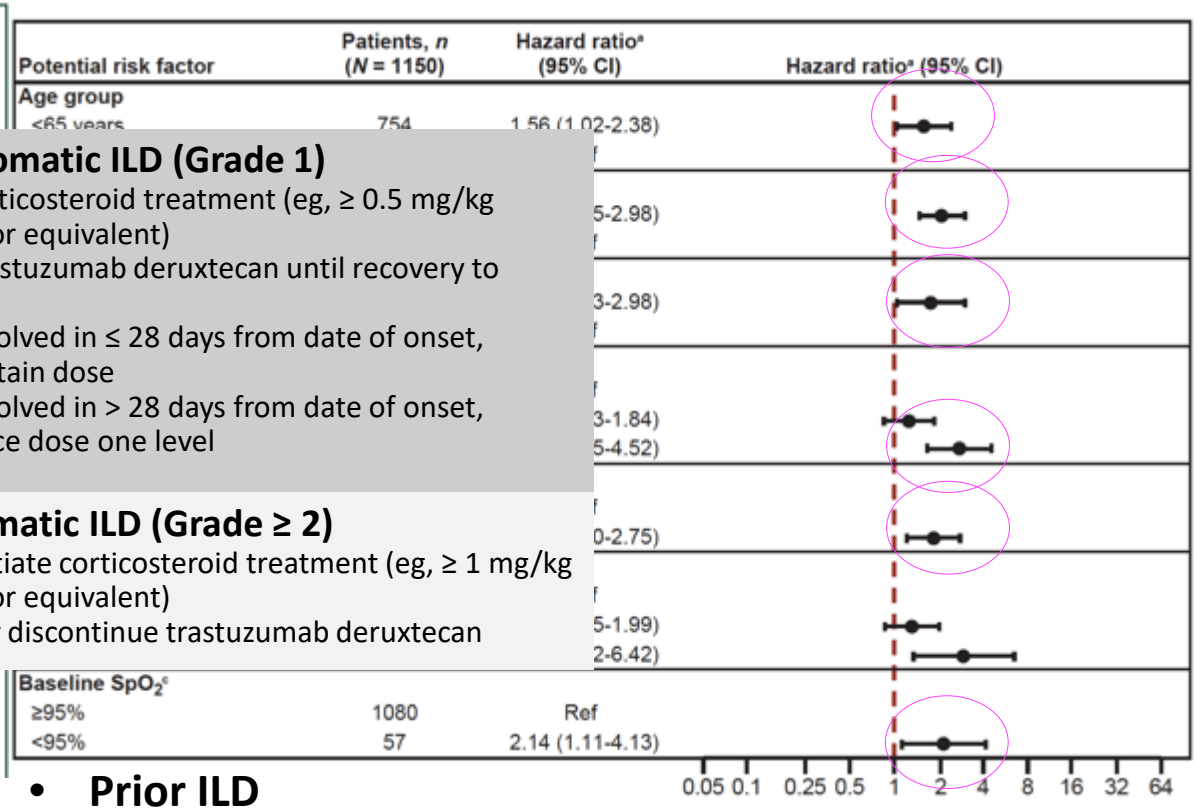
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- **Prior ILD**

- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

Powell et al, ESMO Open 2022; Canellas et al, ESMO 2024

Maintenance Therapy to Prolong Reponse: AFT-38 PATINA Phase 3 Trial of Palbociclib + Anti-HER2 Therapy + ET in HR+/HER2+ MBC

Key Eligibility Criteria
- HR+/HER2+ MBC
- !st line induction therapy
  - 6-8 cycles Rx: tras ± pertuz and taxane/vinorelbine
- No evidence of disease progression

N=518

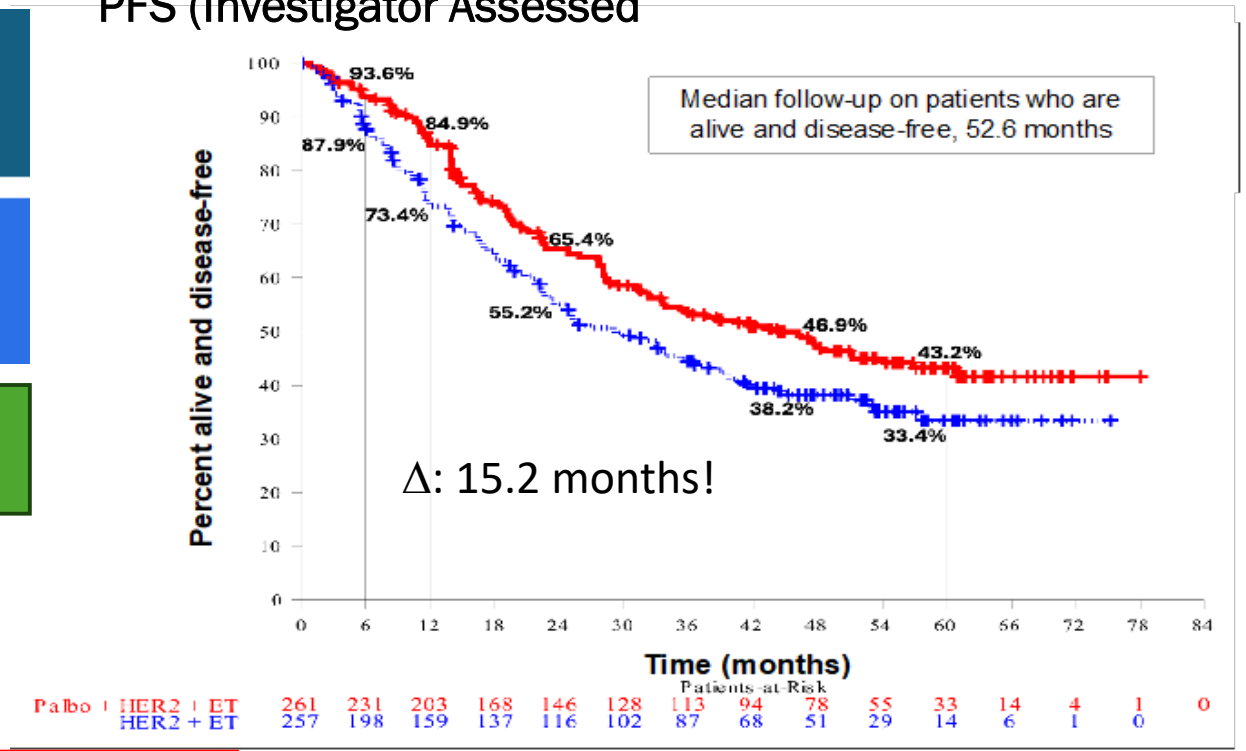
R 1:1

Palbo + Anti-HER2 + ET
Palbociclib (125 mg PO qd D1-D21) + trastuzumab ± pertuzumab + ET[a]

Anti-HER2 + ET
Trastuzumab ± pertuzumab + ET[a]

Primary endpoint: INV-assessed PFS
Key secondary endpoint: OS

PFS (Investigator Assessed



Patient Characteristics, (%) N=518		Palbo + Anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Median age (IQR), years		53.5 (43.6-60.4)	53.0 (45.1-62.8)
Median cycles of induction therapy (range), n		6 (4-8)	6 (4-8)
Pertuzumab use		253 (96.9)	251 (97.7)
Type of ET	AI	237 (90.8)	234 (91.1)
	Fulvestrant	24 (9.2)	23 (8.9)
Prior (neo)adjuvant anti-HER2 therapy	Yes	190 (72.8)	182 (70.8)
	No	71 (27.2)	75 (29.2)
Best response to induction therapy	CR or PR	179 (68.6)	176 (68.5)
	SD	82 (31.4)	81 (31.5)

Additional data
- Improved ORR
- OS early
- Safety: Well tolerated with low discontinuation rates

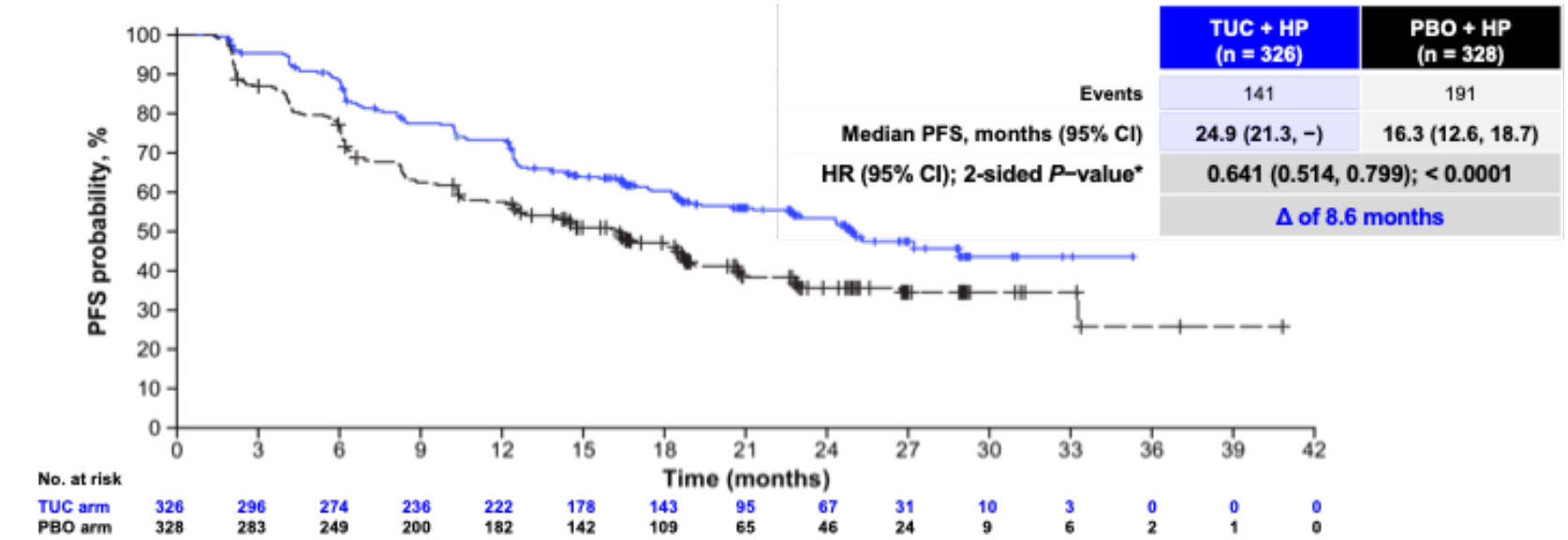
PFS	Palbo + Anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Events	126	136
mPFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
HR (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P*-value	0.0074	

A new SOC where available!

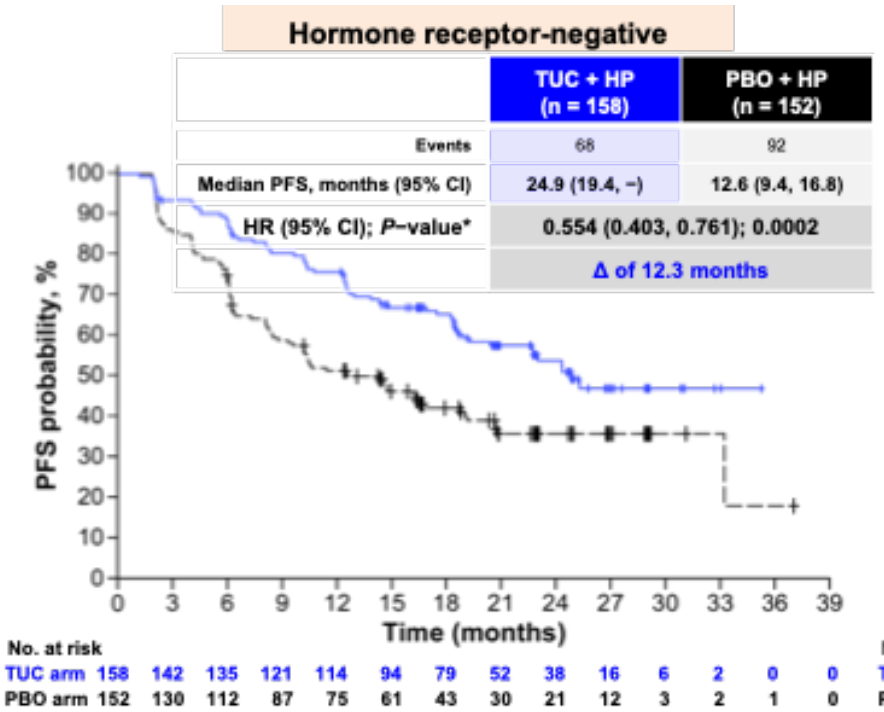
[a] Trastuzumab and pertuzumab were administered per SOC. ET options include an AI or fulvestrant.
Metzger O, et al. NEJM 2026.

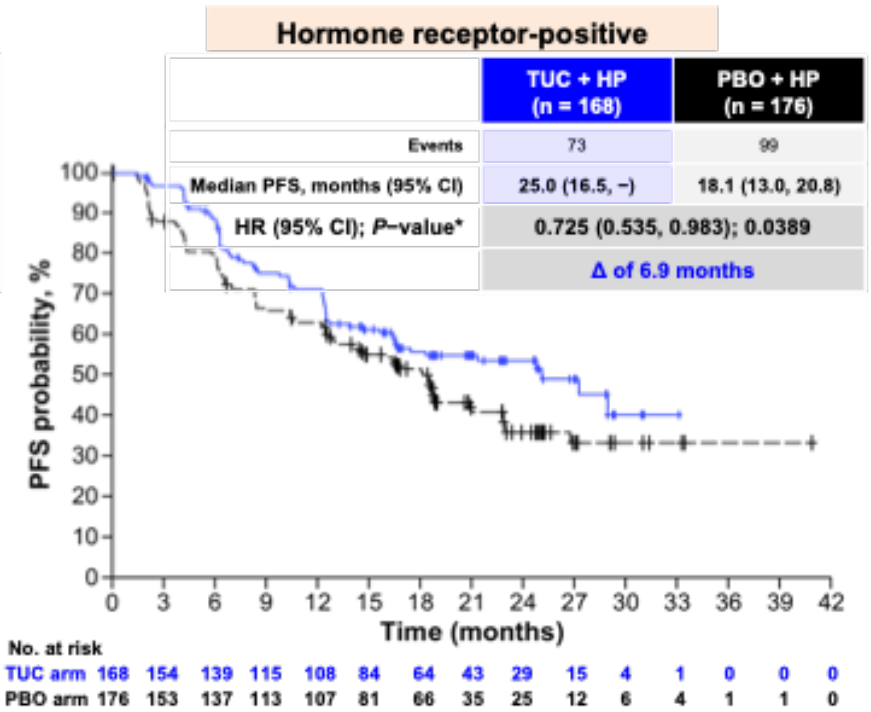
HER2CLIMB-05: Tucatinib as Maintenance Therapy for HER2+ MBC

Potential to reduce brain metastases



Addition of TUC to 1L maintenance therapy extended median PFS to over 2 years in patients with HER2+ MBC, an **8.6-month** improvement over HP, the standard-of-care.





Dieras et al JCO 2026

Optimal Therapy for HER2+ MBC in 2026?

- Accessibility is clearly a key issue around the world; THP remains the standard of care
  - T-DXd has regulatory approval in the US as first-line therapy based on DB09
  - When to use T-DXd in the first-line setting - Early relapse, patients presenting with brain metastases?
  - T-DXd + P is associated with more nausea, less neuropathy than THP
    - Higher mortality by 1%; 0.5% grade 5 ILD
  - Maintenance therapy is a critical question given ongoing nausea with T-DXd/risk of ILD
- Optimal treatment?
  - T-DXd or THP induction, and in those with responding or stable disease followed by:
    - ER+: ET+ trastuzumab/pertuzumab + palbociclib
    - ER-: trastuzumab/pertuzumab + tucatinib
    - Sequencing therapy is a critical issue in interpreting trials and a key factor in improving outcome

1st Line Study	PFS, months	
TH vs THP	18.7	12.4
T-DXd/P vs THP	40.7	26.9
Palbociclib plus ET/HP vs ET/HP in responding pts	44.3	29.1
Tucatinib plus HP in responding pts	24.9	16.3

Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC (DB04)

Clinical Trial Design (Phase III- Destiny-Breast04)

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

R 2:1

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

HR+ ≈ 480
HR− ≈ 60

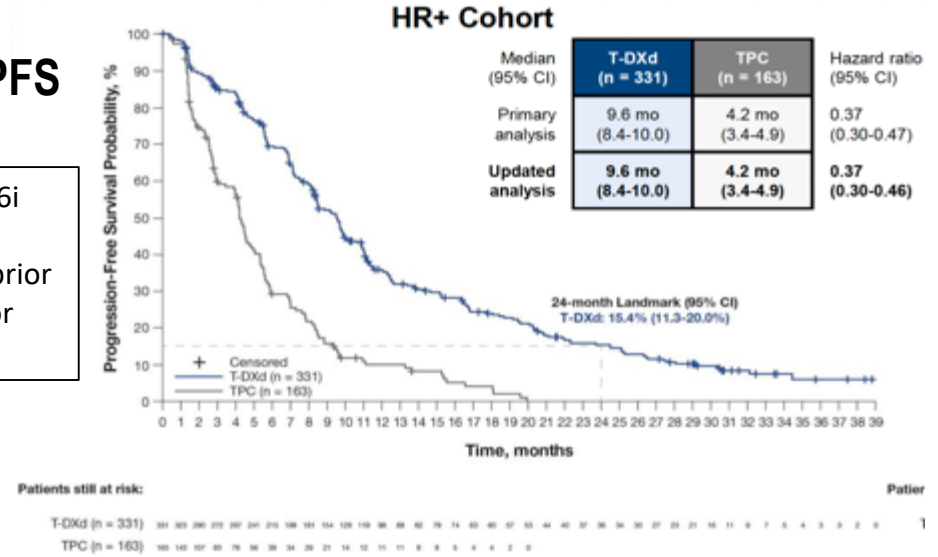
TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

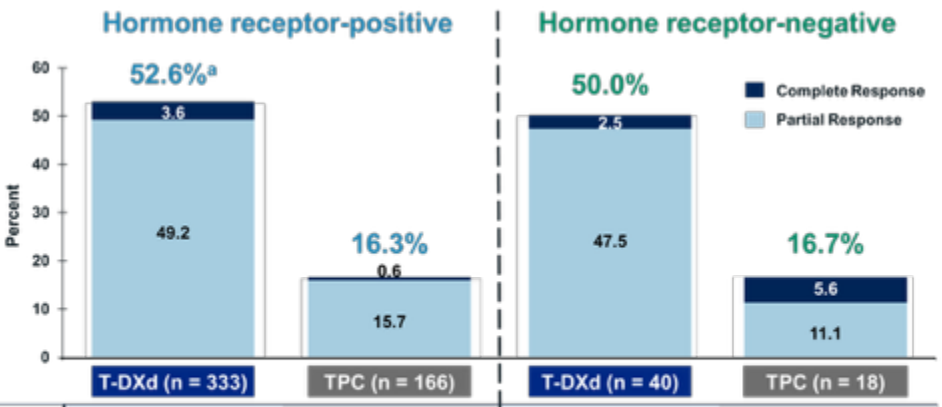
Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

70% prior CDK4/6i
73% liver mets
Median lines of prior chemotherapy for MBC: 1

PFS



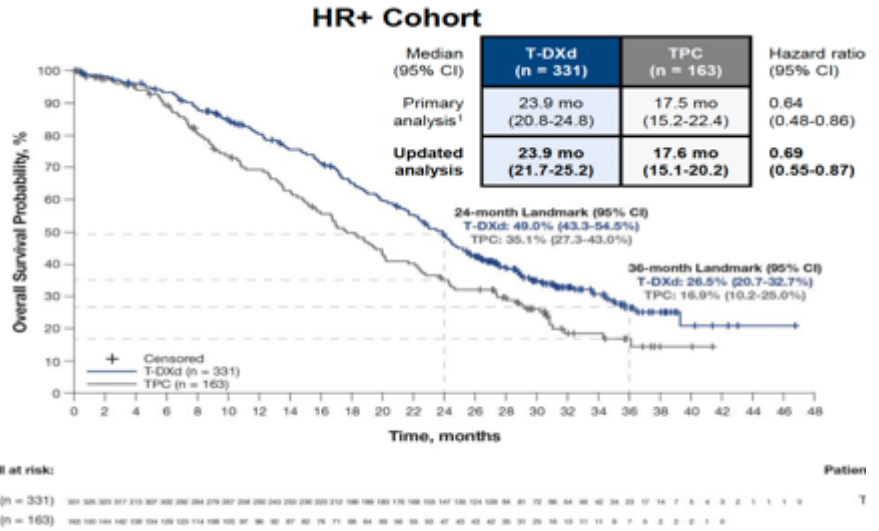
ORR



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive Disease, %	7.8	21.1	12.5	33.3
Not Evaluable, %	4.2	12.7	7.5	5.6
Clinical Benefit Rate[b], %	71.2	34.3	62.5	27.8
Duration of Response, months	10.7	6.8	8.6	4.9

OS

For T-DXd: 8.2% discontinued for ILD/pneumonitis; 4.6% dose reduced for N/V

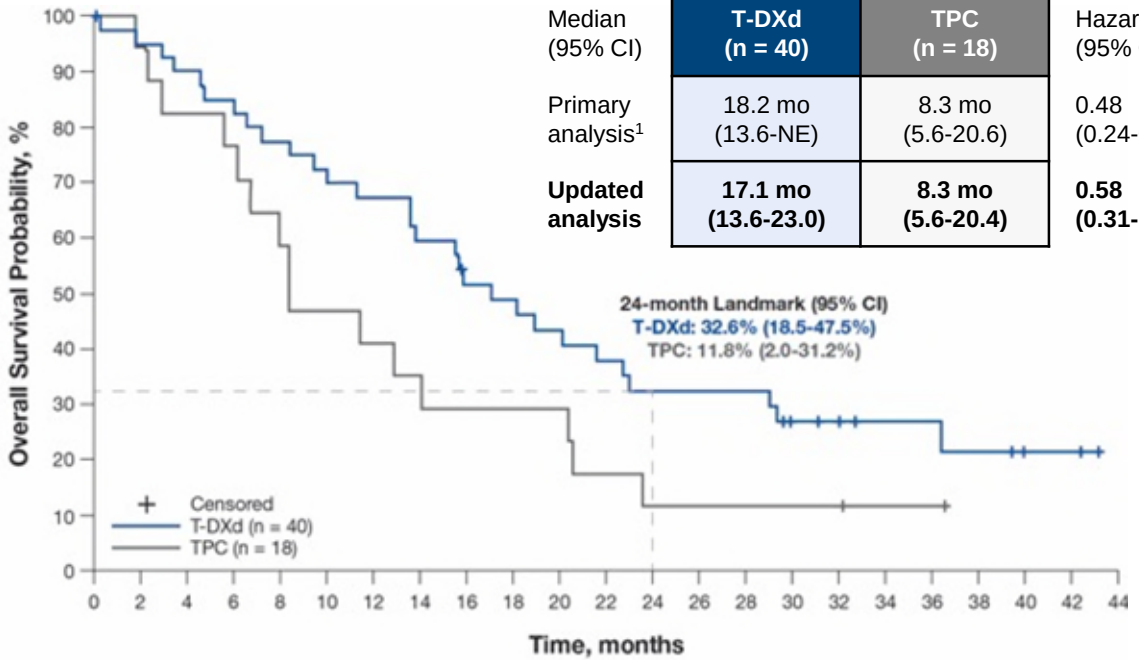


Modi et al, NEJM 2022; ESMO 2023; Nat Med 2025

DESTINY-Breast04: Efficacy in the HER2low/HR− Cohort (Exploratory Analyses)

Overall Survival

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



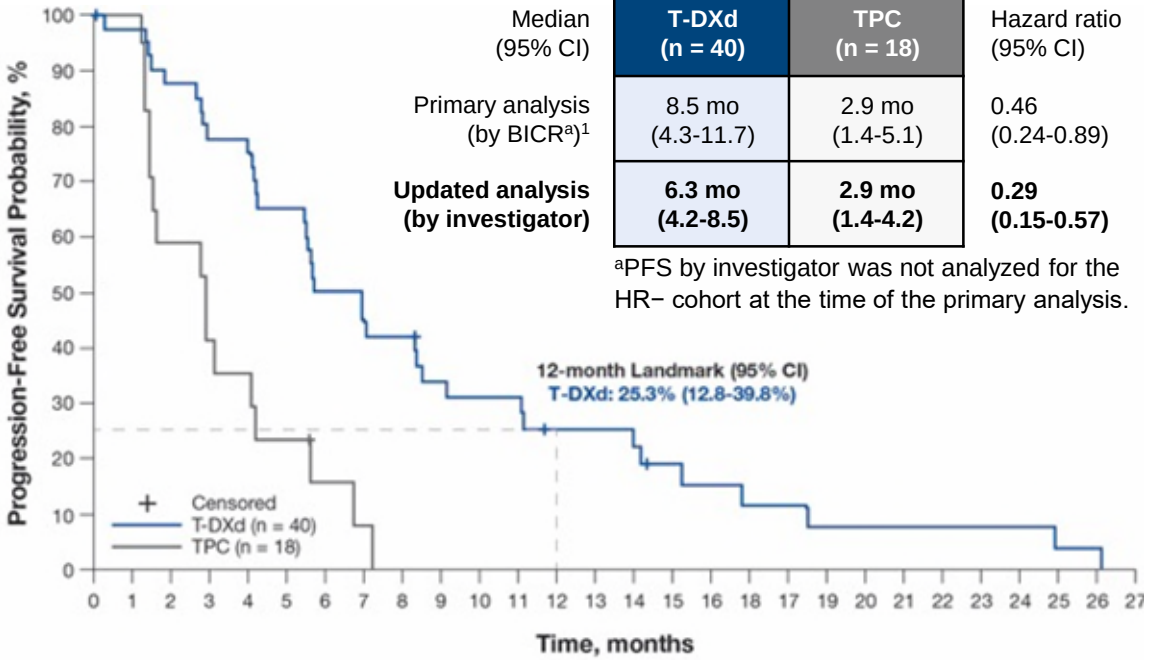
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- Median FU now 32 months vs 18.4 at primary analysis
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

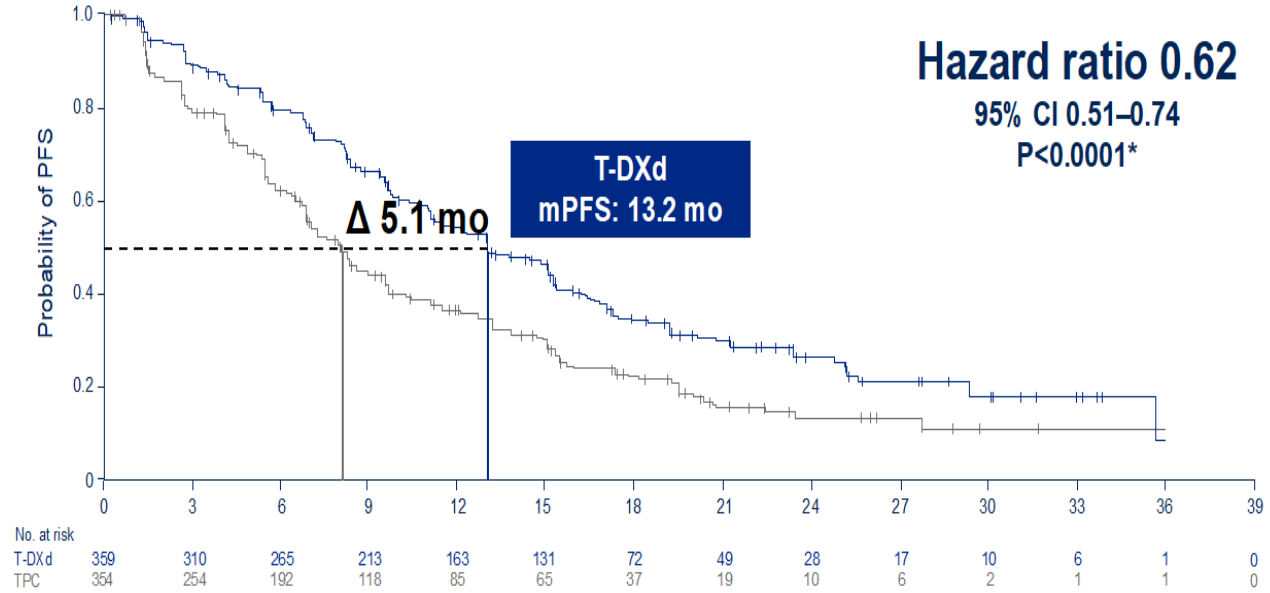
BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi et al, NEJM 2022; ESMO 2023

Destiny Breast-06: PFS in HER2-Low and Ultra-Low

PFS (BICR) in HER2-low

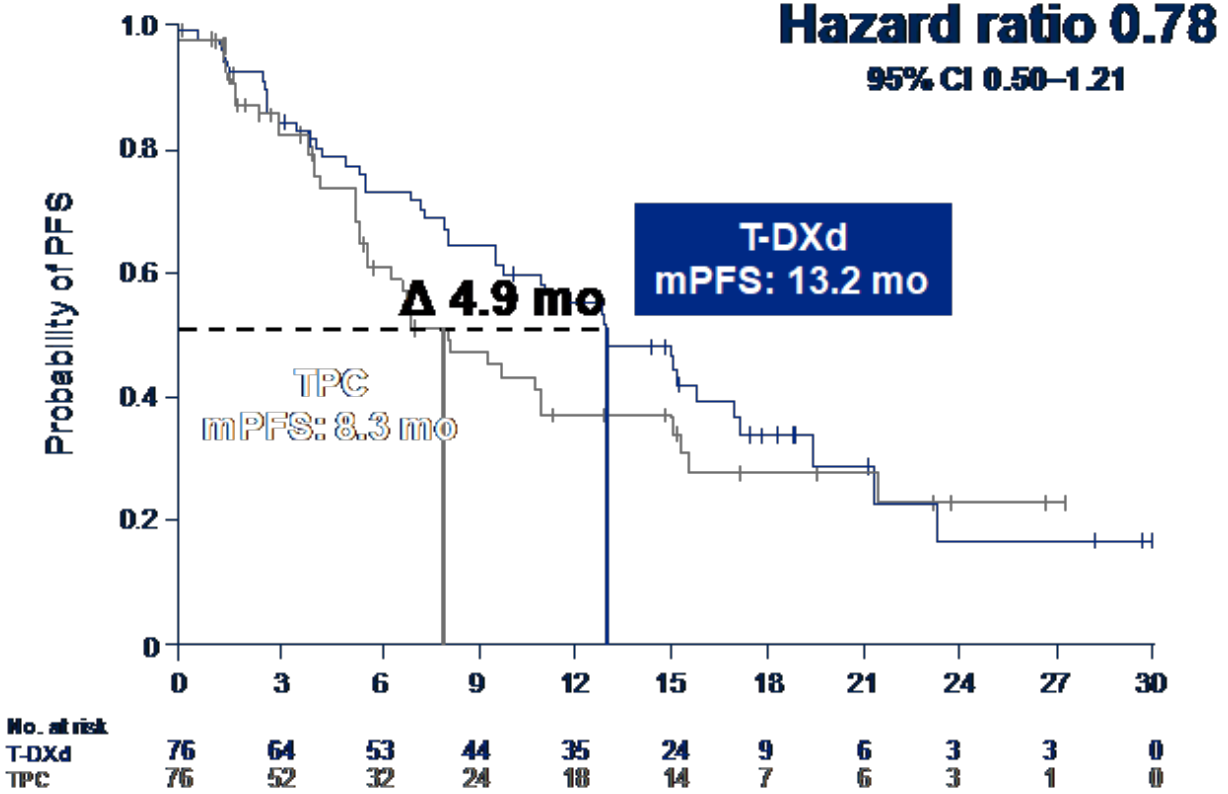
Primary Endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

PFS (BICR) in HER2 ultra-low

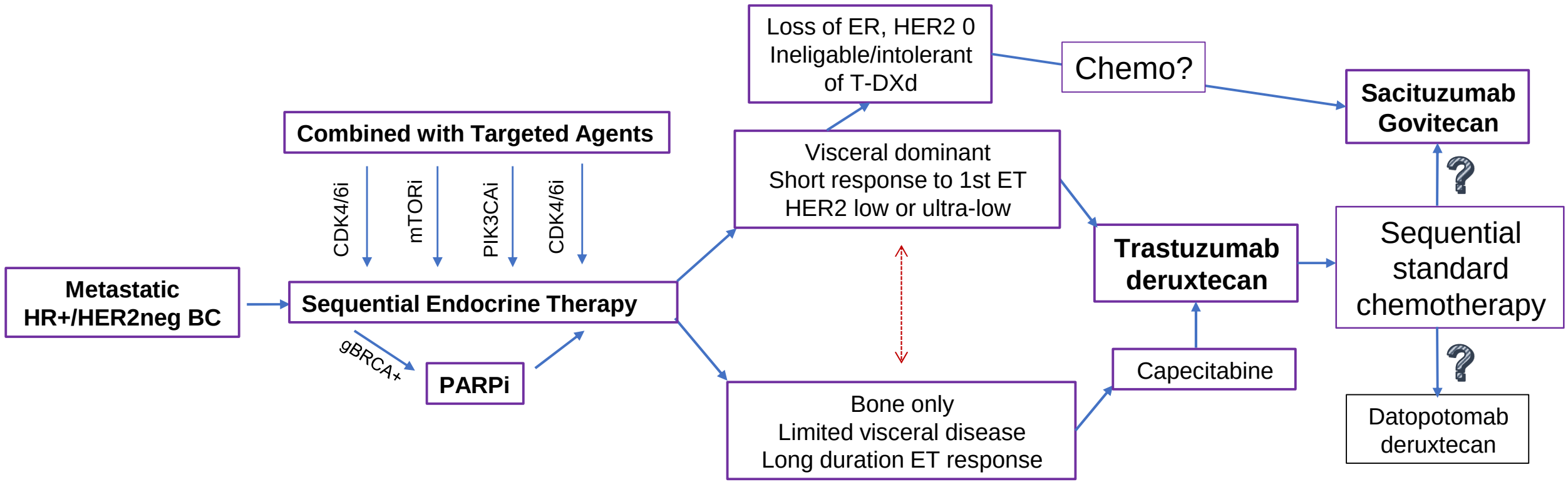
Prespecified exploratory analysis



20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

Bardia et al, NEJM 2024; Curigliano et al, Ann Onc 2026

Roadmap for HR+/HER2- Metastatic Breast Cancer – What do we do Today?



Influenced by organ function, loss of ER, prior chemotherapy exposure

Newer to the treatment paradigm/evolving research:
novel SERMs and SERM combinations, new targeted agents

Maximizing Personalization of Therapy for Early HER2+ Breast Cancer

- Neoadjuvant therapy enables a risk-adapted approach
  - Preferred for almost all patients with HER2+ breast cancer
  - Multiple benefits
    - Less therapy for excellent responders
    - Escalated therapy for poor responders
- Knowledge is power
  - Understanding response allows modification of treatment to:
    - Minimize toxicity and cost
    - Maximize disease free and overall survival
- ASCO guidelines 2021 (Korde et al, JCO 2021)
  - Neoadjuvant therapy should be offered to patients with high-risk HER2+ in whom the finding of residual disease would guide recommendations related to adjuvant therapy
    - Only group where neoadjuvant therapy not *routinely* recommended is T1a, b and N0
- Escalate and de-escalate therapy based on risk and response

COMPASSHER2 TRIALS

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)

- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

Preoperative Phase: all patients

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

No pCR *60%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR

- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

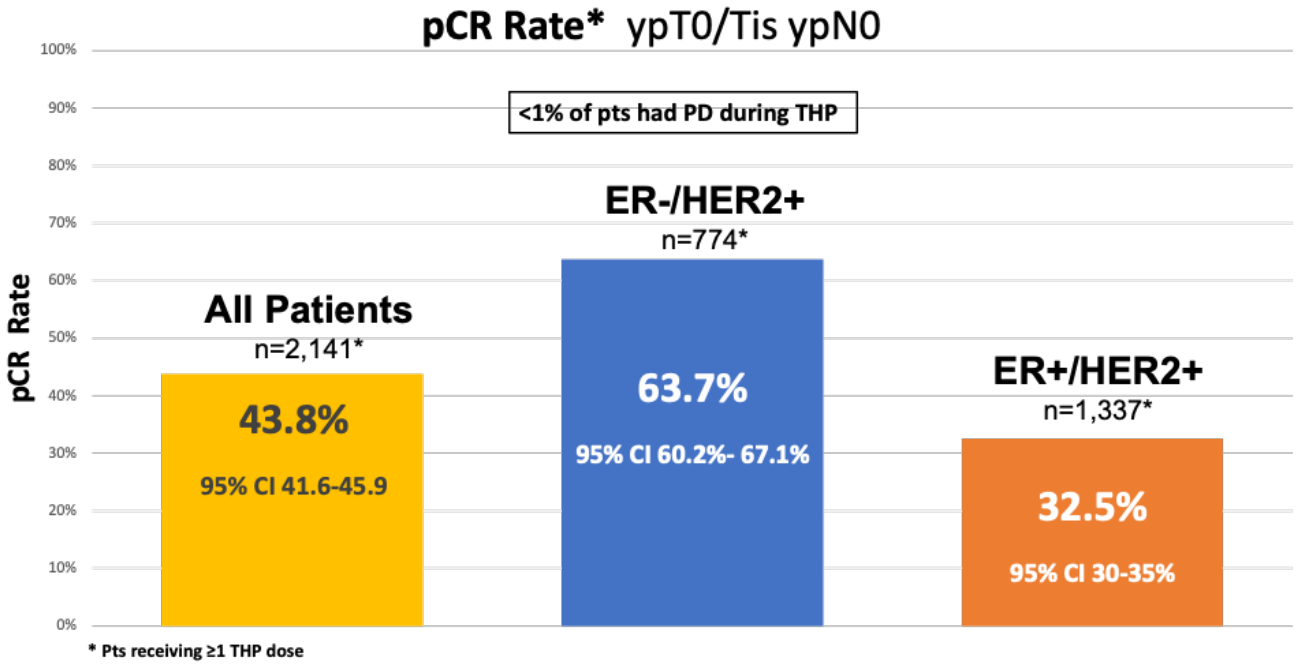
Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration

R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses



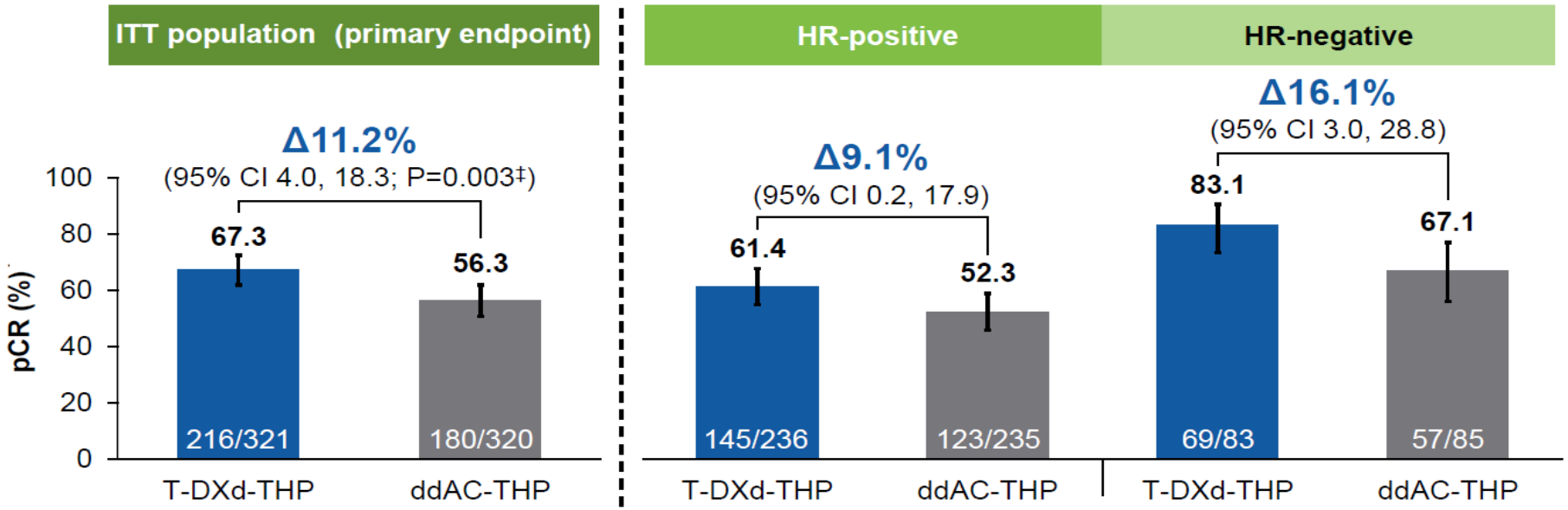
In multivariate analysis, 3 CP factors and 3 molecular markers were associated with pCR

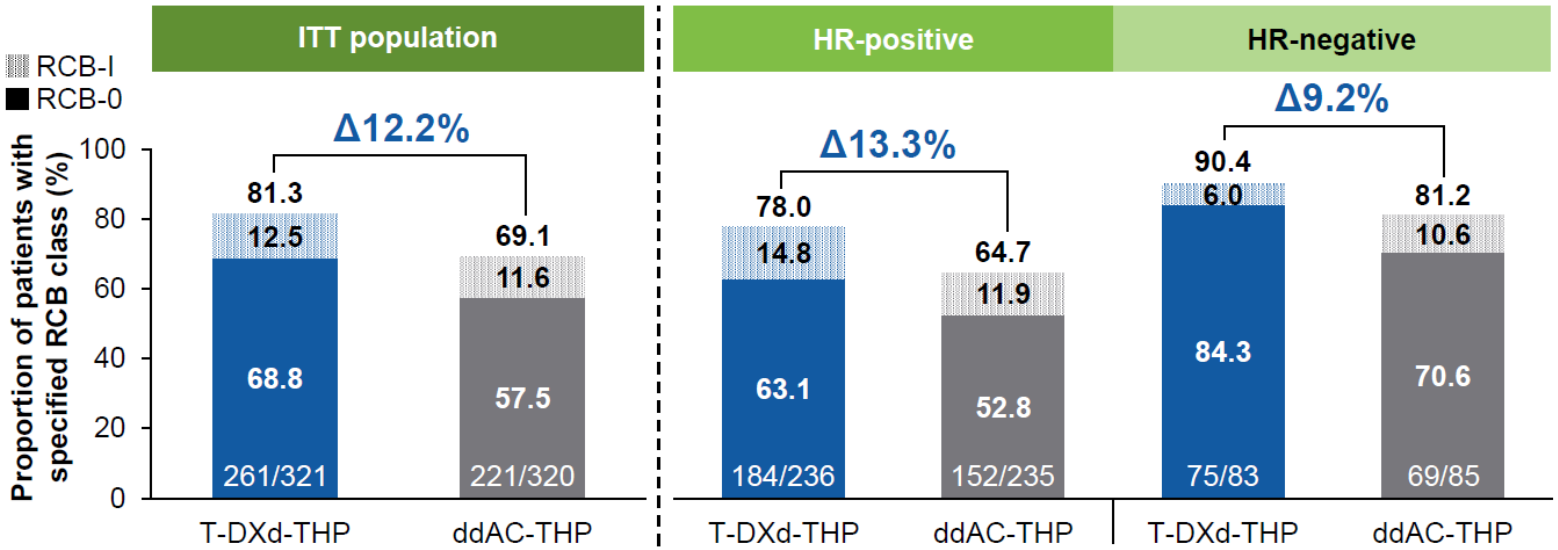
Clinical Factor/Biomarker		OR for pCR (95% CI)	# patients
ERBB2 mRNA level			
	ERBB2/10 units	**1.33 (1.16-1.51)**	569
Intrinsic subtype			
	non-HER2E	1.0	216
	HER2E	**2.69 (1.63-4.42)**	353
IgG			
	IgG/10 units	**1.09 (1.02-1.16)**	569
ER	ER+ >70%	1.0	244
	ER 11-70%	**2.71 (1.39-5.27)**	64
	ER 1-10%	**2.89 (1.14-7.33)**	31
	ER-	**4.21 (2.57-6.91)**	230
HER2 IHC			
	2+/ISH+	1.0	85
	3+	**2.74 (1.14-6.59)**	461
Taxane			
	docetaxel	1.0	188
	paclitaxel	**1.76 (1.12-2.75)**	368

- HER2Dx pCR likelihood score
  - 27 genes: immune activation, luminal differentiation, tumor cell proliferation, HER2 amplicon
    - 569 out of 2141 patients had testing available
    - High HER2DX pCR score associated with a ~40% higher absolute pCR rate compared to a low score

	ER- (n=230)		ER+ (n=339)	
HER2Dx score	**n (%) of pts**	**pCR rate**	**n (%) of pts**	**pCR rate**
High	**147 (64%)**	**70%**	**36 (11%)**	**58%**
Low	**13 (6%)**	**31%**	**214 (63%)**	**18%**
p value		***p <0.01***		***p <0.01***

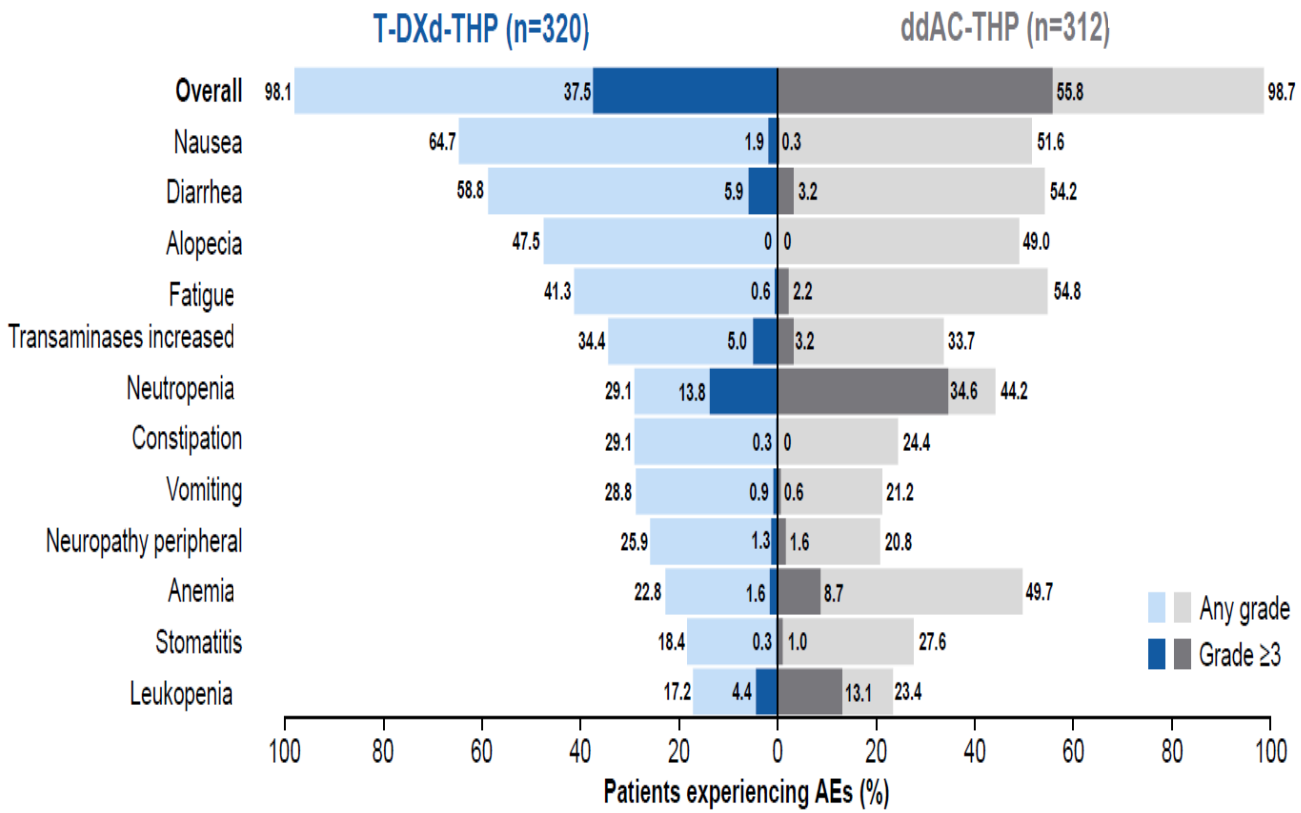
DESTINY-Breast11: pCR and RCB with T-DXd-THP vs AC-THP





Harbeck N, et al. Ann Oncol 2025

DESTINY-Breast11 Phase 3 Trial of Neoadjuvant T-DXd Alone or Followed by THP vs SOC for High-Risk HER2+ EBC: Safety



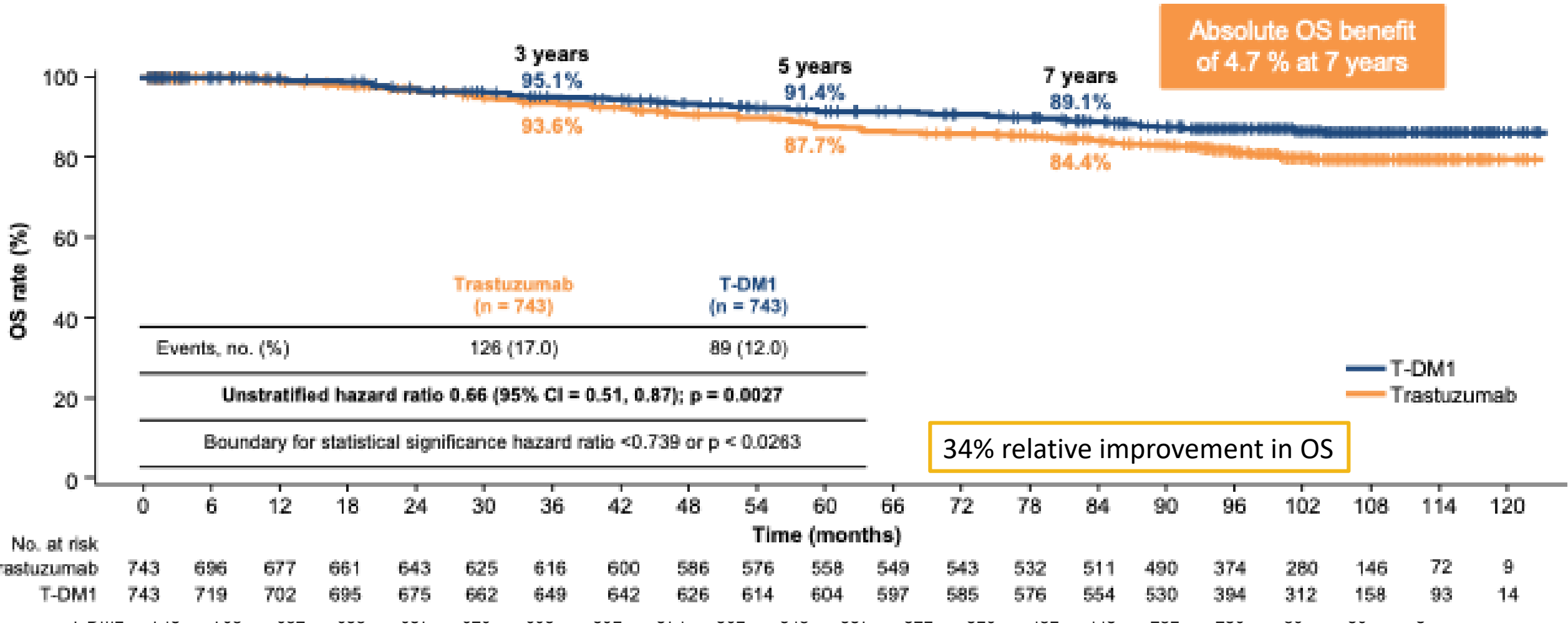
Safety Overview, n (%)	T-DXd-THP (n=320)	ddAC-THP (n=312)
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any SAE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death[a]	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)
Grade ≥3	1 (0.3)	6 (1.9)
Grade 5	0	0
AE leading to surgical delay[b]	11 (3.4)	8 (2.6)

Monitoring:

- High-resolution CT chest scans: Q6W during treatment; if ILD/pneumonitis was suspected on T-DXd, treatment was interrupted and a full investigation completed
- Echocardiograms or multigated acquisition scans: during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess LVEF

Harbeck N, et al. Ann Oncol 2025.

Improving Post-Neoadjuvant Therapy for HER2+ ESBC
KATHERINE OS Final Analysis; Median Follow-up 8.4 Years (101 months)



* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

First benefit see at median FU of 3.4 years

Loibl et al, SABCS 2023; Geyer et al, NEJM 2025

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Hitting the Mark — Individualizing Therapy for HER2-Positive Early-Stage Breast Cancer

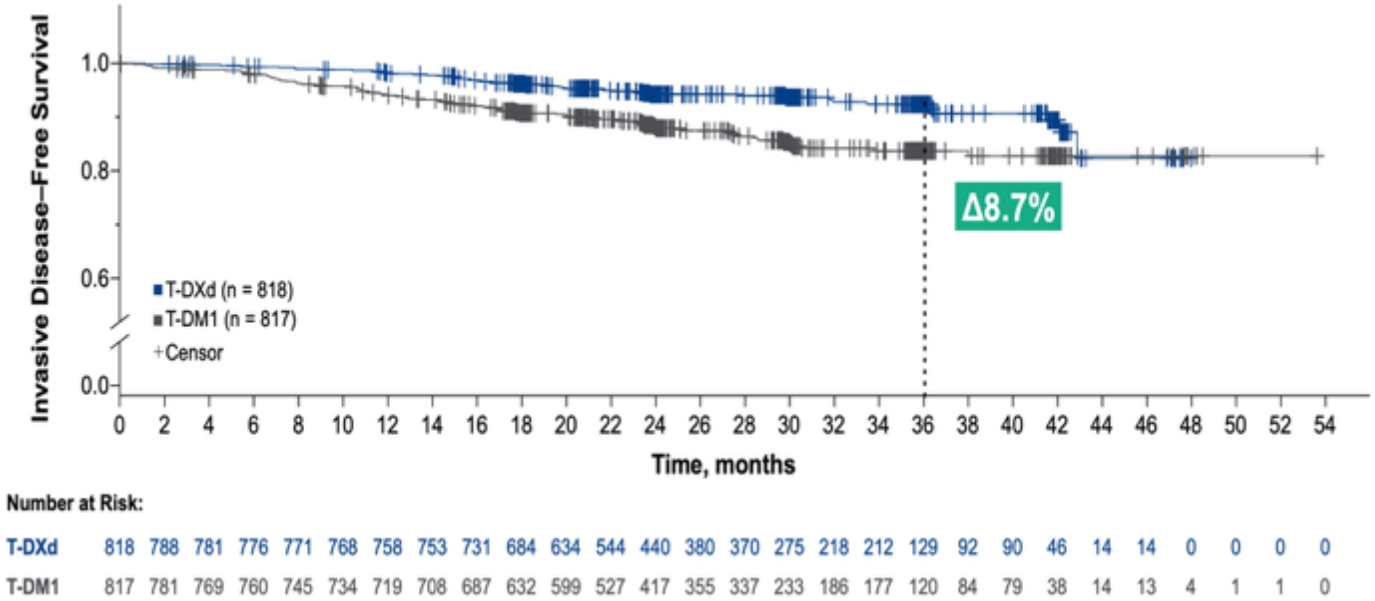
Hope S. Rugo, M.D.[1]

N Engl J Med 2026;394:918-920

DESTINY-Breast05: IDFS with T-DXd vs T-DM1 in High-Risk HER2+ EBC

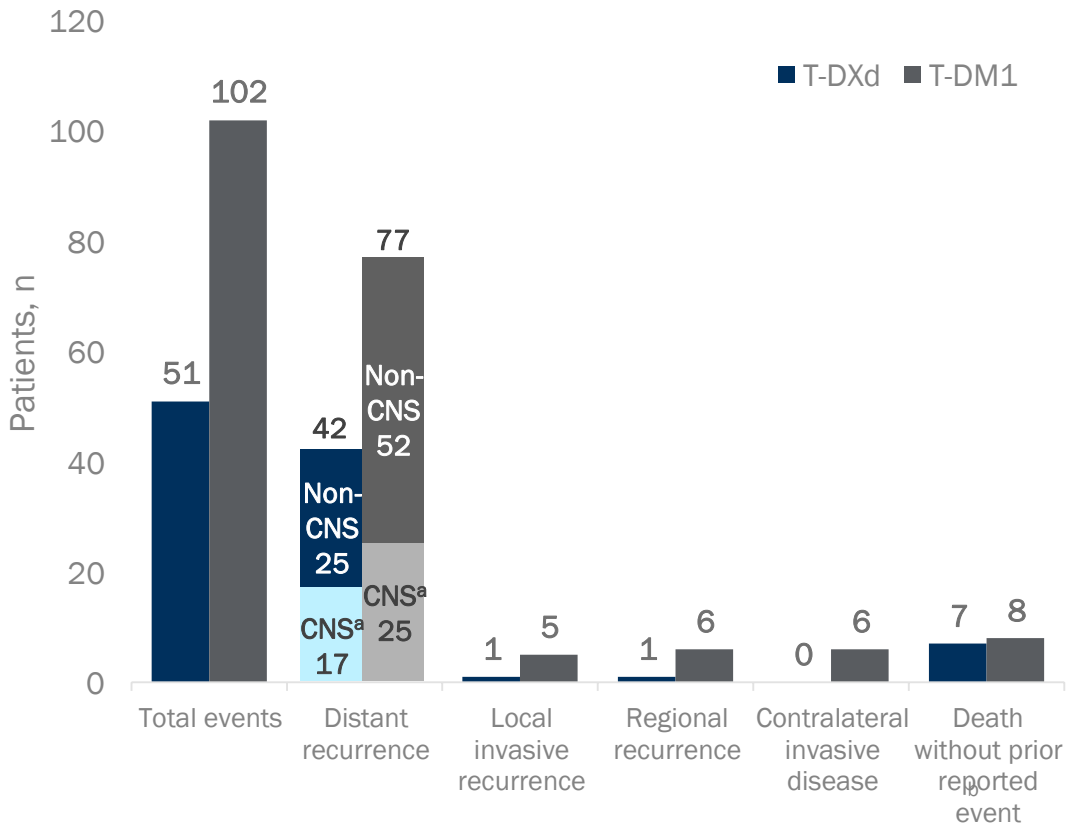
Benefit see at median FU of 30 mo

IDFS



Outcome Measure	T-DXd (n=818)	T-DM1 (n=817)
Patients with events, n (%)	51 (6.2)	102 (12.5)
3-year IDFS, % (95% CI)	92.4 (89.7-94.4)	83.7 (80.2-86.7)
HR (95% CI)	0.47 (0.34-0.66)	
P value	<0.0001	

Categories of First IDFS Events



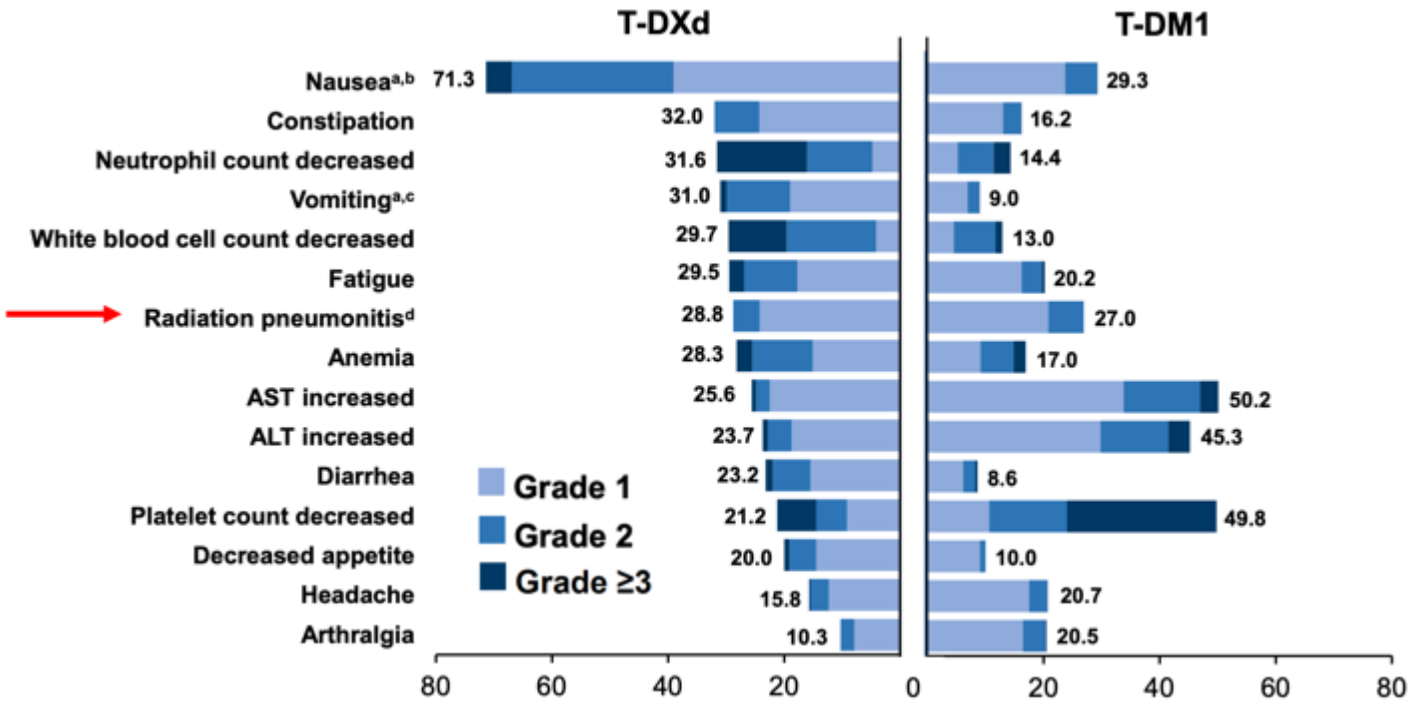
[a] CNS as sole site for distant recurrence or one of multiple distant recurrent sites. [b] Causes of death in the T-DXd arm were 2 drug-related ILD, unrelated respiratory tract infection, acute respiratory failure (outside AE reporting period), acute respiratory distress syndrome (outside AE reporting period), and 2 disease progression, and in the T-DM1 arm were drug-related sepsis, unrelated ovarian cancer, unrelated aneurysm, unrelated pneumothorax, unrelated leiomyosarcoma, self-inflicted gun wound, and 2 disease progression.

Geyer CE, et al. ESMO 2025. Abstract LBA1; Loibl et al, NEJM 2025

Absolute improvement in DFS: 8.8%

Interim Analysis of DESTINY-Breast05 : Safety

TEAEs in ≥20% of Patients



	T-DXd (n=806)	T-DM1 (n=801)
Grade ≥3 TEAEs, n (%)	408 (50.6)	416 (51.9)
Serious TEAEs	140 (17.4)	109 (13.6)
TEAEs associated with discontinuation	144 (17.9)	103 (12.9)
TEAEs associated with drug interruptions	400 (49.6)	329 (41.1)
TEAEs associated with deaths*	3 (0.4)	5 (0.6)
Treatment-related deaths	2 (0.2)	1 (0.1)
Median treatment duration (months)	9.8	9.7
Patients completed 14 cycles (%)	72.3	76.3
ILD (adjudicated), n (%)	77(9.6)	13 (1.6)
grade ≥3 ILD	9 (1.1)	0 (0)
grade 5 ILD	2 (0.3%)	0 (0)
LV dysfunction	23 (2.9)	14 (1.7)

Safety Overview		T-DXd (n=806)[a]	T-DM1 (n=801)[a]
Overall TEAEs	Any grade	802 (99.5)	788 (98.4)
	Grade ≥3	408 (50.6)	416 (51.9)
	Serious	140 (17.4)	109 (13.6)
	Associated with drug d/c	144 (17.9)	103 (12.9)
	Associated with deaths	3 (0.4)	5 (0.6)
Adjudicated Drug-related ILD[b]	Any grade	77 (9.6)	13 (1.6)
	Grade 1	16 (2.0)	8 (1.0)
	Grade 2	52 (6.5)	5 (0.6)
	Grade 3	7 (0.9)	0
	Grade ≥4	2 (0.2)[c]	0
LV Dysfunction	Any grade	23 (2.9)	14 (1.7)
	Grade 1	1 (0.1)	0
	Grade 2	20 (2.5)	11 (1.4)
	Grade 3	2 (0.2)	3 (0.4)
	Grade ≥4	0	0

[a] Prophylactic antiemetics were recommended but not mandatory. [b] In the T-DXd and T-DM1 arms: 39.1% and 23.7% grade 1, 27.8% and 5.5% grade 2, and 4.5% and 0.1% grade 3 events, respectively. [c] In the T-DXd and T-DM1 arms: 19.0% and 6.9% grade 1, 10.9% and 2.0% grade 2, and 1.1% and 0.1% grade 3 events, respectively. [d] In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1 and 4.6% and 6.1% grade 2 events,
Geyer CE, et al. ESMO 2025. Abstract LBA1; Loibl et al, NEJM 2025

How do we Incorporate T-DXd into Treatment for Early HER2+ Breast Cancer?

- Neoadjuvant T-DXd
  - Appealing to improve the rate of pCR for high-risk cancers
    - DB11 included all node positive disease, along with inflammatory and T3
    - Only 4 doses of T-DXd, lowest rate of ILD reported to date (still with low mortality)
    - High rate of pCR in ER+ disease (dominant group in post-neoadjuvant studies)
- Post-neoadjuvant T-DXd
  - Limits potential ILD risk only to those at highest risk of recurrence; expands efficacy
    - Node positive or inoperable at presentation
    - Low treatment related mortality
    - Efficacy in low HER2/ISH+; disease where HER2+ cells are limited at surgery
    - Possible benefit: decreasing CNS relapse?
    - Long duration of therapy post surgery
- At present, and with regulatory approval
  - DB11 for high risk/high disease burden
  - Start with THP (or TH for stage I), rescue with T-DXd pre-op for lower risk disease
  - If residual disease following TCHP or THP, rescue with T-DXd post-operatively
    - It appears to be safe to give concomitant radiation with T-DXd
    - Optimal management of toxicity is critical
- Next steps
  - Imaging and ctDNA to individualize response
    - Early clearance of ctDNA correlates with pCR and EFS in multiple studies
    - MRI functional tumor volume plus biopsy highly correlates with pCR

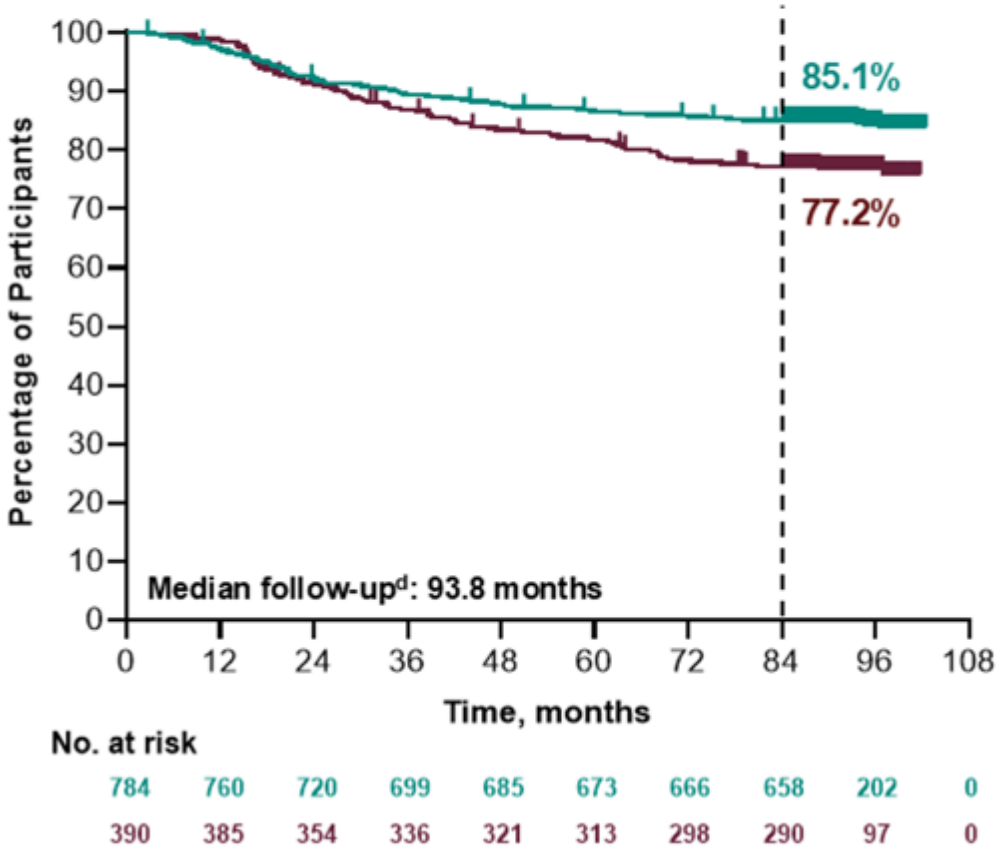
Individualizing therapy will help cure more patients with high risk HER2+ ESBC

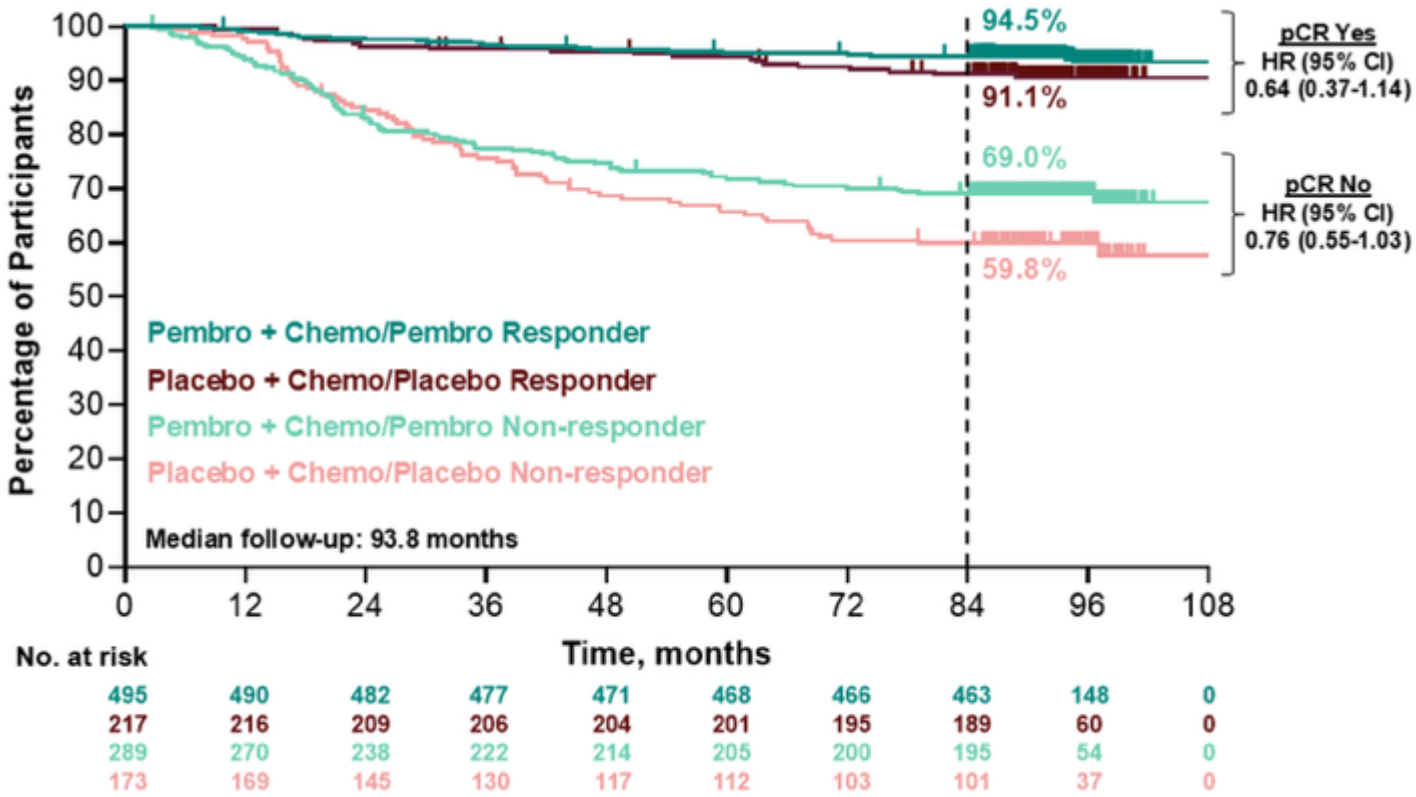
Examples of Major Advances

Improving Outcome for TNBC

KEYNOTE 522: Overall Survival and OS by pCR

FA	Events	HR (95% CI)
Pembro + Chemo/Pembro	15.3%	0.64[a] (0.49-0.85)
Placebo + Chemo/Placebo	23.1%	

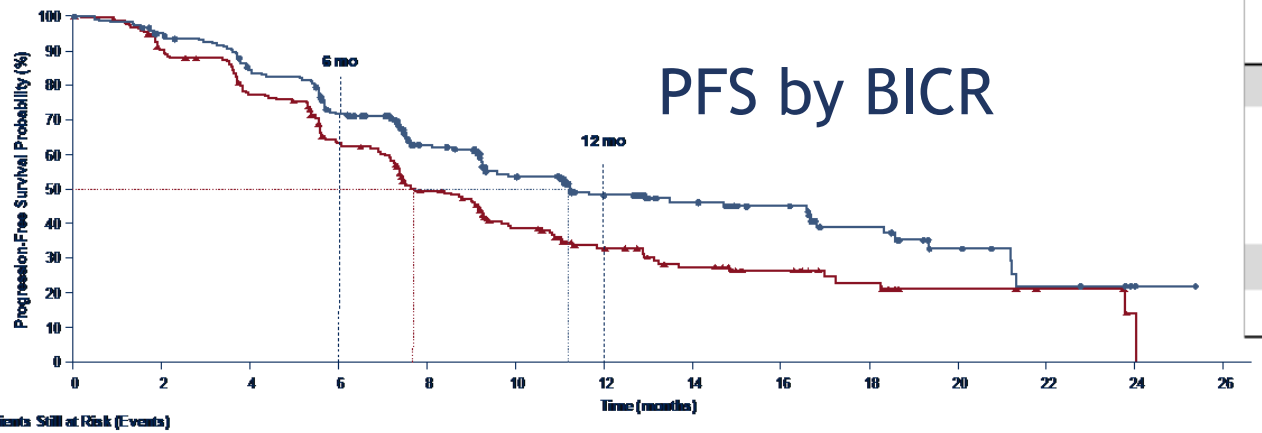




Greatest impact of pembrolizumab on EFS for RCB2
(Pusztai et al, Ann Oncol 2024)

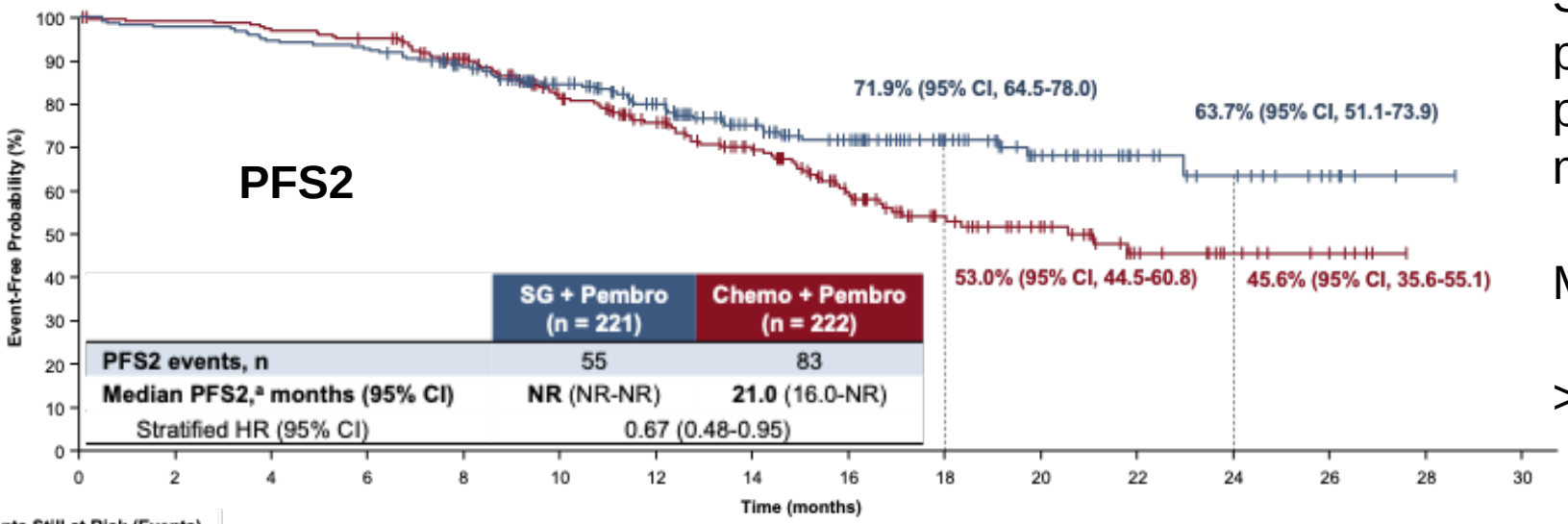
Schmid et al, ASCO 2026

PFS 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)

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



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
PFS2 events, n	55	83
Median PFS2,[a] months (95% CI)	**NR** (NR-NR)	**21.0** (16.0-NR)
Stratified HR (95% CI)	0.67 (0.48-0.95)	

PFS2 was longer in the SG + pembro group compared with the chemo + pembro group despite the high rate of crossover in the chemo + pembro group, with a 33% reduction in risk of a PFS2 event with SG + pembro

ASCENT-04:
Sacituzumab govitecan plus pembrolizumab vs chemotherapy plus pembrolizumab for PD-L1+ mTNBC

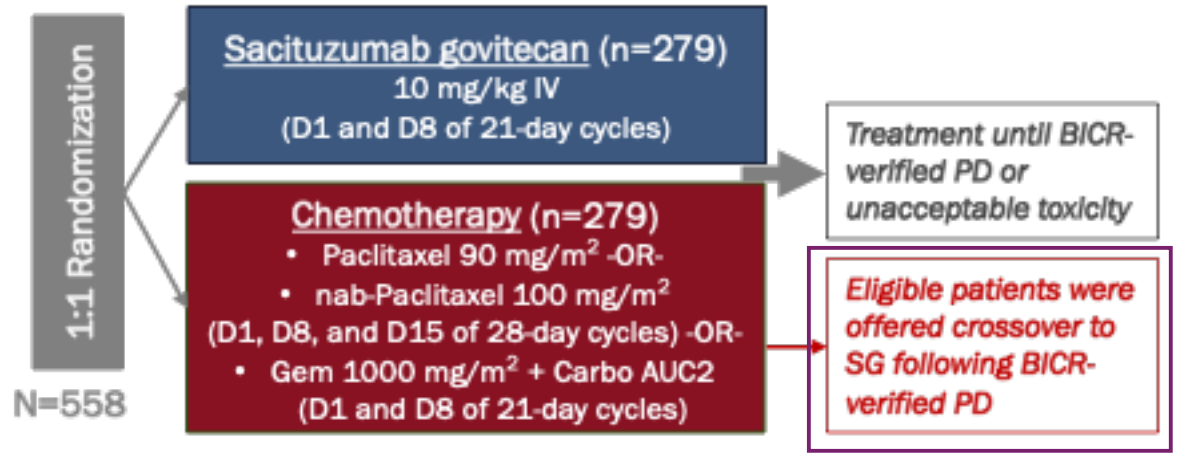
Median FU 14 mo.

>80% cross-over to SG in 2nd line

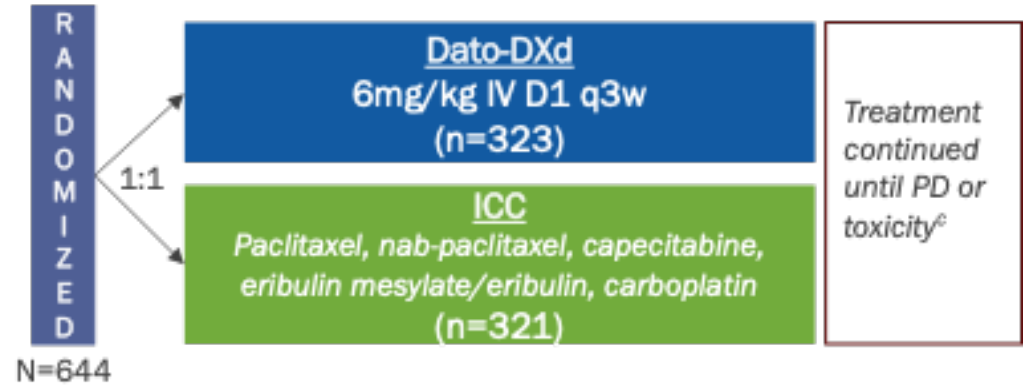
Understanding Sequencing: Does it Matter?

Recent Trials for TNBC 1st line

ASCENT-03: Cortes et al



TROPION-Breast02: Dent et al

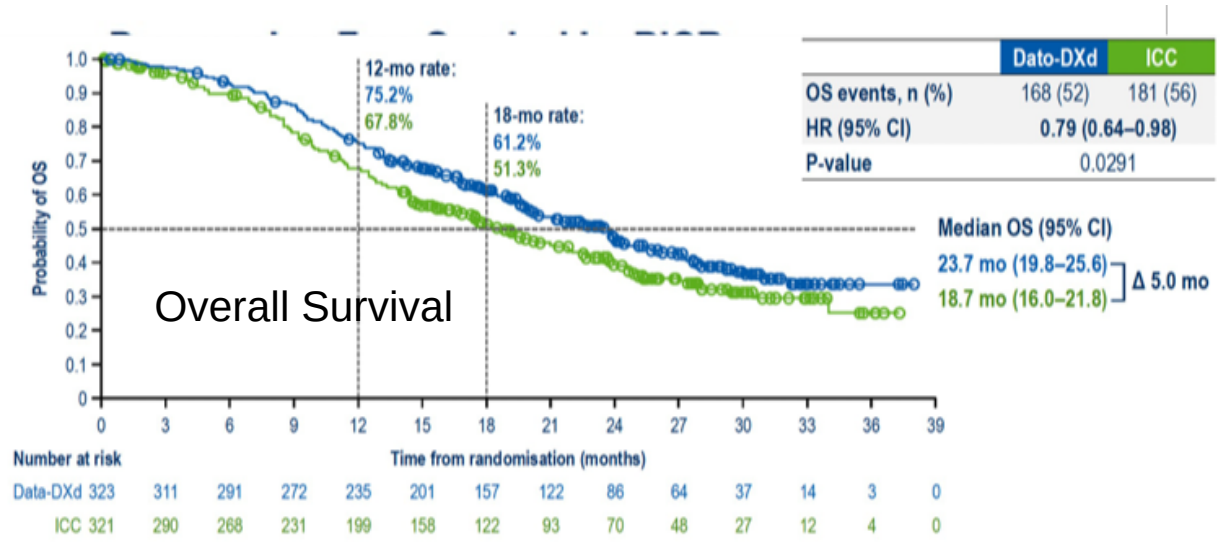


Descriptive OS

- Median follow-up: 13.2 months (range, <0.1-29.2)
- OS not yet mature (37%)
- Eligible patients were offered crossover to SG following BICR-verified PD
  - Of 179 patients who initiated subsequent treatment after Chemo, 147 (82%) received SG

Stratified HR (95% CI)	0.98 (0.75-1.30)

SG demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo by BICR analysis, with a 38% reduction in risk of disease progression or death



TROP2 ADC Trials in 1L mTNBC (PD-L1- or aPD-(L)1 ineligible)

	ASCENT-03[1]	TROPION Breast-02[2]
Arms	SG vs. Chemo Chemo: paclitaxel/nab-paclitaxel/gem+carbo	Dato-DXd vs. Chemo Chemo: *paclitaxel, nab-paclitaxel, capecitabine, eribulin, carboplatin (single agent)*
Schedule		**y cycle)**
Crossover		ded
Median Follow-up (mo)		
mPFS (mo) *HR*		s 5.6
mOS (mo) *HR*		s 18.7
Adverse events	**Neutropenia; GI toxicities**	**Oral mucositis; ocular toxicities**
ADC post progression	85%	41%
PD-L1+	1%	10%

Sequencing clearly matters and should be routinely incorporated into phase III trials; also avoids disparities in access

However, this approach is faced with significant challenges including cost (much higher for experimental agents) and need for drug production as well as data interpretation

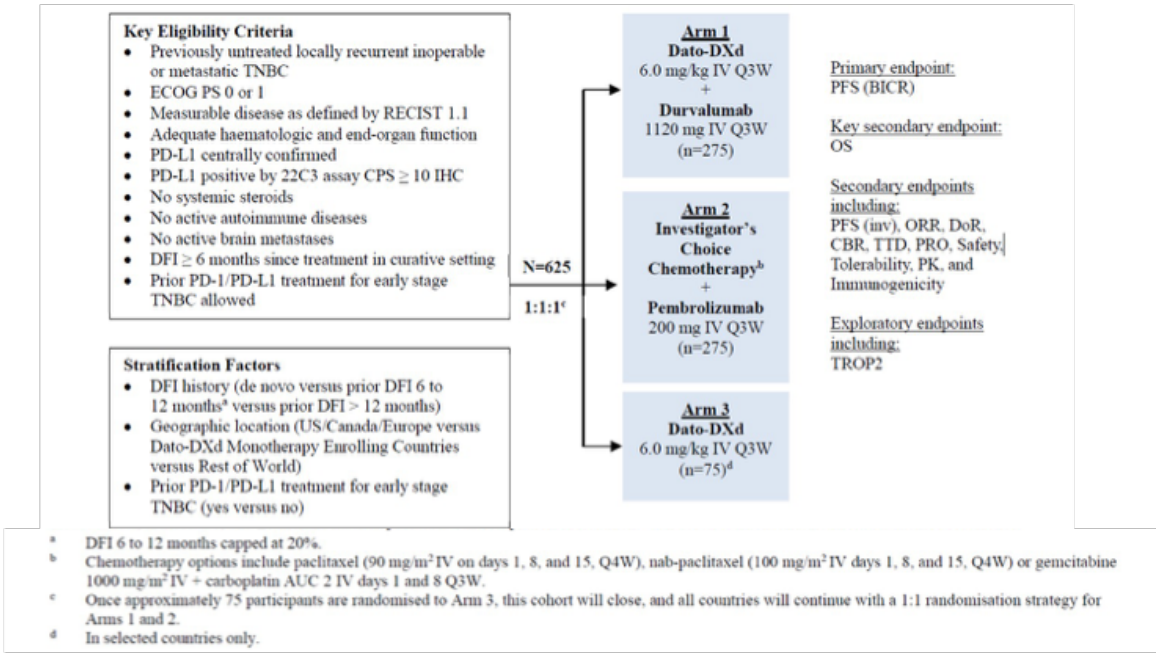
Not a cross trial comparison

1. Cortes et al. ESMO 2025; NEJM 2025 2. Dent et al. Ann Oncol 2026

Ongoing Combination Studies for mTNBC

TROPION Breast05: PD-L1+ Datopotomab Deruxtecan in mTNBC (N=625)

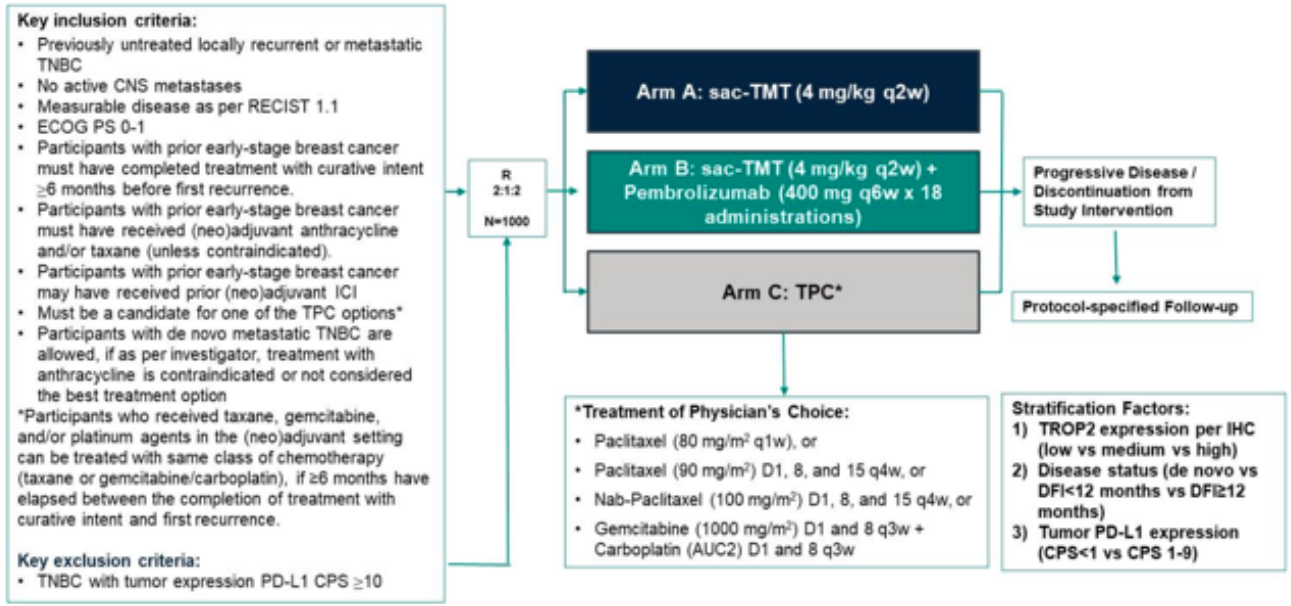
NCT06841354



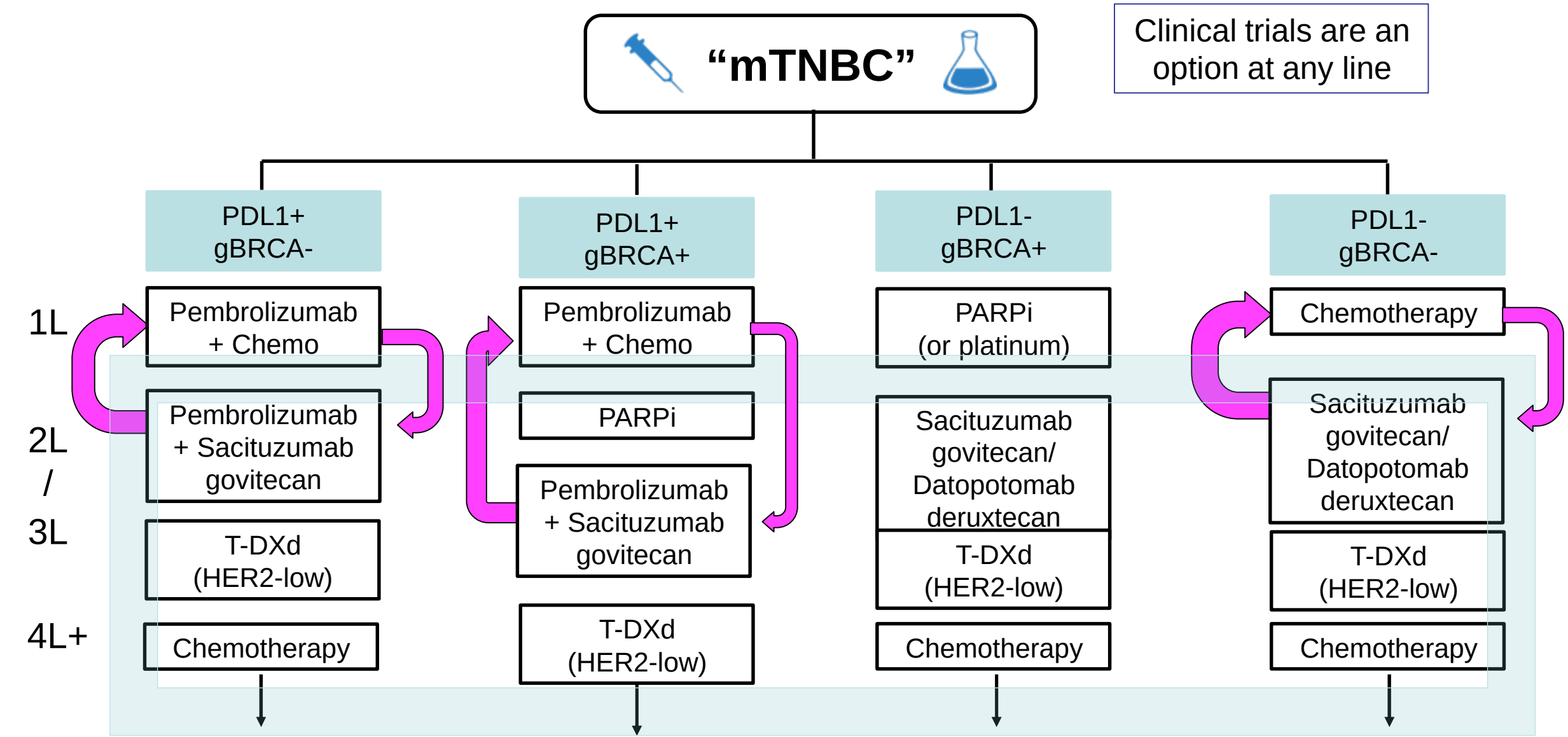
[a] DFI 6 to 12 months capped at 20%.
[b] Chemotherapy options include paclitaxel (90 mg/m² IV on days 1, 8, and 15, Q4W), nab-paclitaxel (100 mg/m² IV days 1, 8, and 15, Q4W) or gemcitabine 1000 mg/m² IV + carboplatin AUC 2 IV days 1 and 8 Q3W.
[c] Once approximately 75 participants are randomised to Arm 3, this cohort will close, and all countries will continue with a 1:1 randomisation strategy for Arms 1 and 2.
[d] In selected countries only.

TroFuse 11: PD-L1- Sacituzumab Tirumotecan in mTNBC (N=1000; CPS<10)

NCT06841354



A New Paradigm for 2026



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

The Future for TNBC

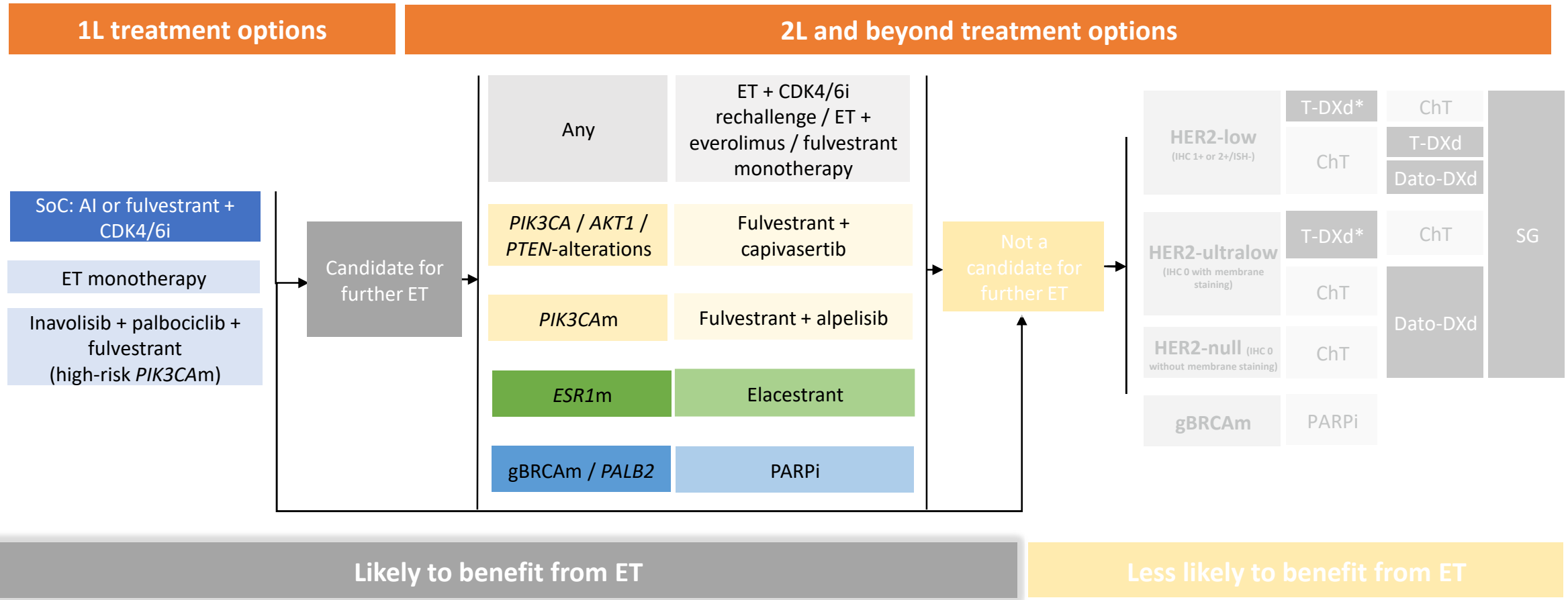
- Significant progress in the treatment of TNBC
- Future and ongoing directions
  - Individualizing therapy based on a better understanding of appropriate biomarkers
    - Expanding the use of antibody drug conjugates
    - Further enhancing the host immune response with optimal combination therapy
      - Bispecific antibodies: Targeting PD-L1/PD-1 and VEGF
      - New ADCs: New targets (Nectin-4, B7H4), new payloads (MMAE/F, etc)
      - Radioligands
  - Neoadjuvant therapy for all but the smallest tumors
    - De-escalating and escalating therapy based on response
    - Improving post-neoadjuvant therapy

Examples of Major Advances

Oral SERDs, Molecular Markers of Resistance

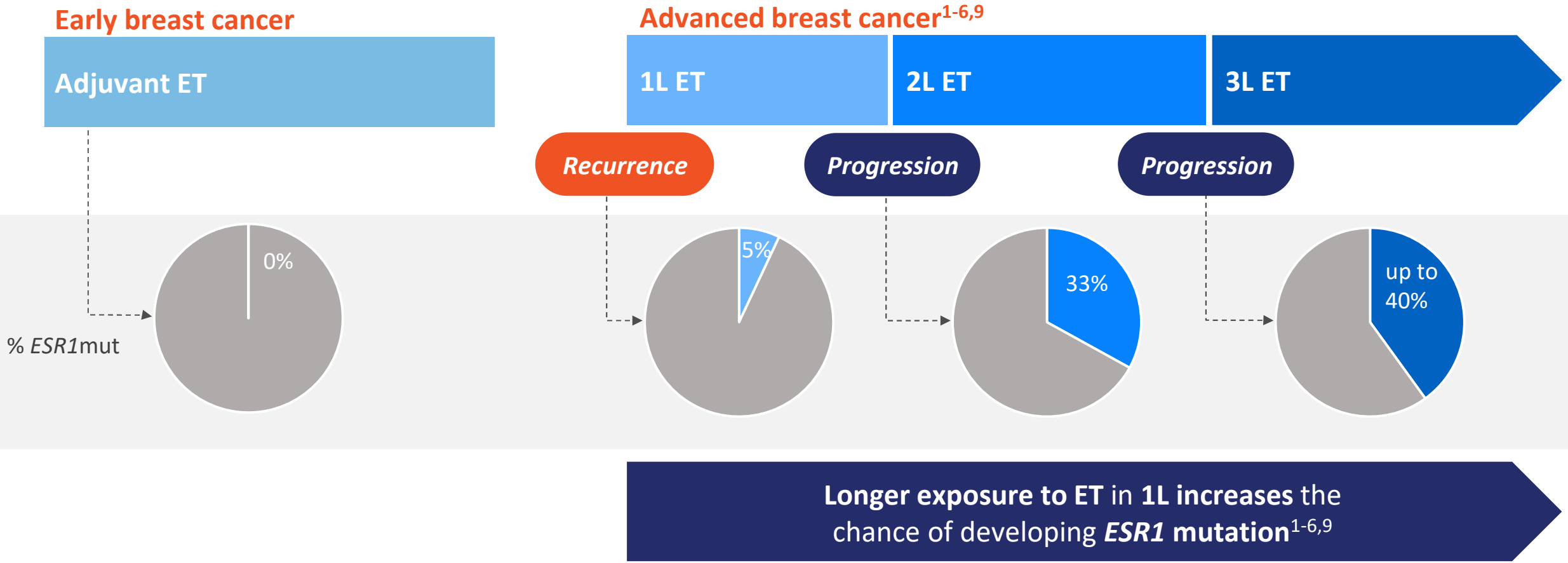
New Targeted Therapy!

Combination Therapy with ET and a Targeted Agent for HR+, HER2- aBC is now a SOC for Most Patients



*T-DXd may be used for HER2 IHC 0+ 1+ or 2+/ISH negative, previously treated with at least one line of endocrine-based therapy in the metastatic setting.
1L/2L=first-/second-line; aBC=advanced breast cancer; AKT1=AKT serine/threonine kinase 1; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ChT=chemotherapy; Dato-DXd=datopotamab deruxtecan; ET=endocrine therapy; ESR1m=estrogen receptor 1 gene mutation; gBRCAm=germline BRCA mutation; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PALB2=partner and localizer of BRCA2; PARPi=poly (ADP-ribose) polymerase inhibitor; PIK3CA=phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN=phosphatase and tensin homolog; SG=sacituzumab govitecan; T-DXd=trastuzumab deruxtecan.
See slide notes for references.

Most *ESR1 M*utations Arise After Progression on 1L mBC Therapy[1-9]

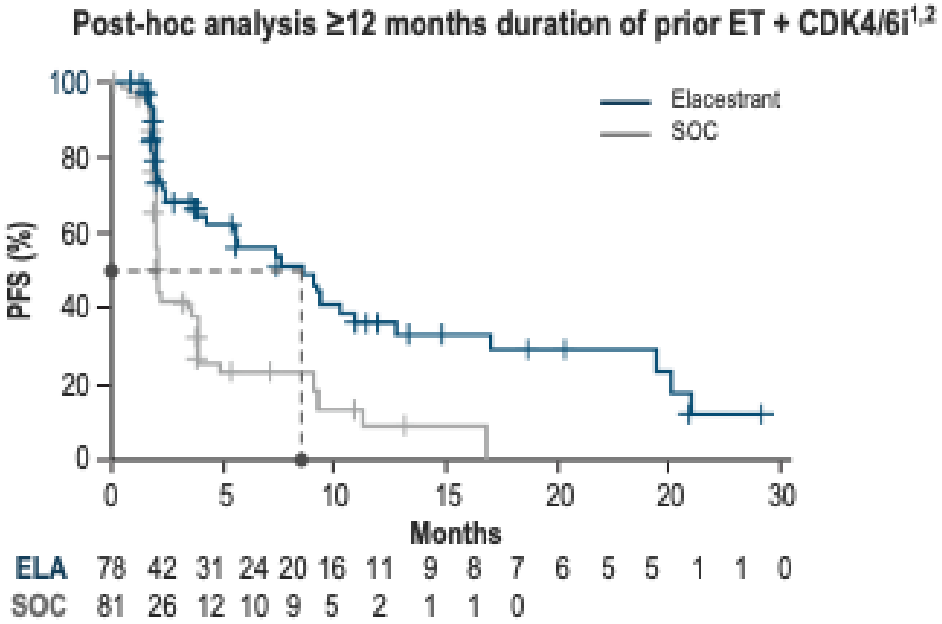


Abbreviations: 1L, first line; 2L, second line; 3L, third line; ESR1, estrogen receptor 1; ET, endocrine therapy; mBC, metastatic breast cancer

1. Jeselsohn R, et al. *Clin Cancer Res.* 2014;20:1757-1767. 2. Jeselsohn R, et al. *Cancer Cell.* 2018;33:173-186. 3. Allouchery V, et al. *Breast Cancer Res.* 2018;20:40; 4. Schiavon G, et al. *Sci Transl Med.* 2015;7;313ra182. 5. Brett JO, et al. *Breast Cancer Res.* 2021;23:85. 6. Callens C, et al. *Anal Chem.* 2022;94:6297-6303. 7. Robinson DR, et al. *Nat Genet.* 2013;45:1446-1451. 8. Reinert T, et al. *Front Oncol.* 2017;7:26. 9. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256.

EMERALD: mPFS in *ESR1*-mut patient with endocrine sensitivity[1–3]

mPFS was 7.3 mo in patients with liver and/or lung mets, and 5.5 mo in those with *ESR1* and *PIK3CAmut* tumors[1,2]



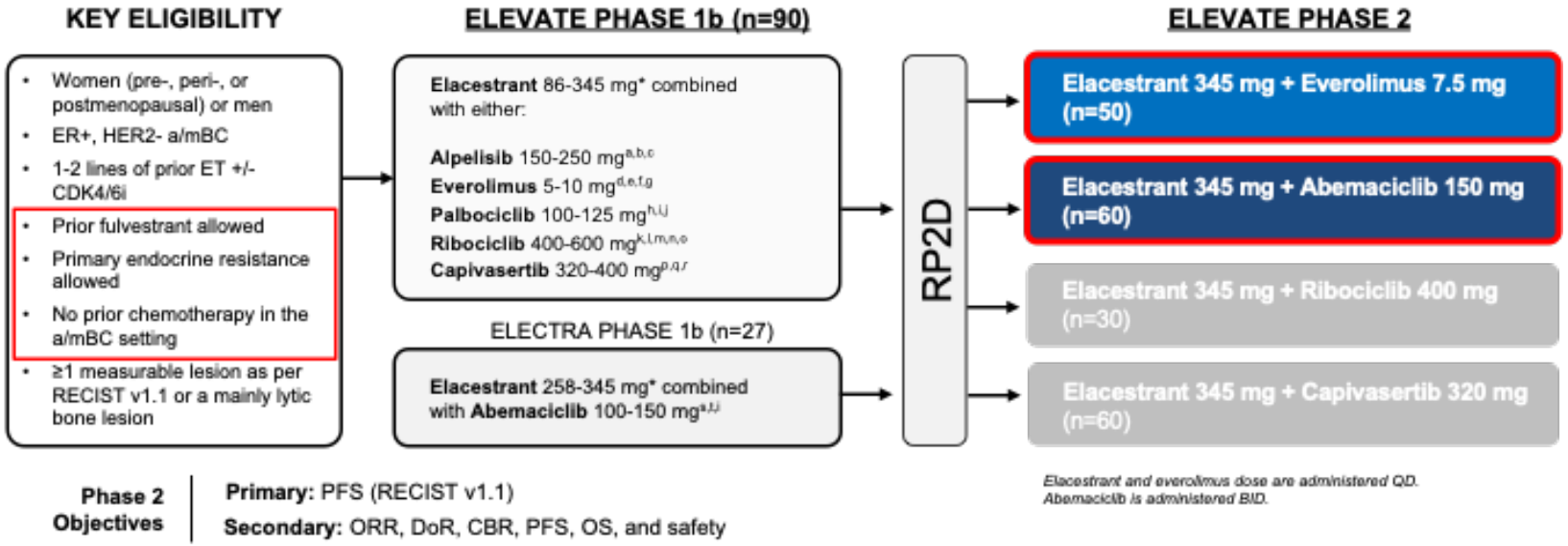
	Elacestrant (n=78)	SOC (n=81)
mPFS, mo	8.6	1.9
Absolute difference, mo	+6.7	
HR [95% CI]	0.41 [0.26–0.63]	

ESR1-mut PFS overall 3.8 vs 1.9 mo (HR 0.55; 0.39-0.77, p=0.005)

Patients with ≥12 months of prior ET + CDK4/6i	% (n)	Elacestrant mPFS, months	SOC mPFS, months	HR [95% CI]
All *ESR1*-mut patients	**100** (159)	**8.6**	**1.9**	**0.41** [0.26–0.63]
PIK3CA-mut[a]	**39** (62)	**5.5**	**1.9**	**0.42** [0.18–0.94]
Bone metastases[b]	**86** (136)	**9.1**	**1.9**	**0.38** [0.23–0.62]
Liver and/or lung metastases[c]	**71** (113)	**7.3**	**1.9**	**0.35** [0.21–0.59]
≥3 metastatic sites[d]	**33** (53)	**10.8**	**1.8**	**0.31** [0.12–0.79]
TP53-mut	**38** (61)	**8.6**	**1.9**	**0.30** [0.13–0.64]
HER2−low expression[e]	**48** (77)	**9.0**	**1.9**	**0.30** [0.14–0.60]

Calculated with covariates. This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.
[a]Includes 545K, H1047R, E542K, and others. [b]85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement). [c]55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement). [d]The number of metastatic sites was available for 135 of 159 patients with ESR1-mutated tumors and prior ET + CDK4/6i ≥12 months. [e]Locally assessed HER2 immunohistochemistry score of 1+ and 2+ with no in situ hybridization amplification. Data not available for all patients.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mPFS, median progression-free survival; mut, mutation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC, standard of care; TP53, tumor protein 53.
1. Bardia A, et al. *Clin Cancer Res*. 2024;30(19):4299–4309; 2. Bardia A, et al. SABCS 2022. Abstract GS3–01; 3. Bardia A, et al. SABCS 2024. P1-01-25.

Elevate: Phase II Study of Elacestrant in Combination with Everolimus or Abemaciclib



- Ela/Eve
  - **PFS 8.3 mo (4-10.2)**
  - 82.9% DCR
  - 19.5% ORR
  - 8.54 mo mDOR

	Elacestrant + everolimus	
Subgroup	**N**	**mPFS, months (95% CI)**
All patients	*50*	**8.3** [4.0-10.2]
Visceral disease	*36*	**7.7** [3.7-9.4]
No prior fulvestrant	*25*	**8.3** [4.2-12.9]
No primary endocrine resistance	*40*	**8.3** [4.0-12.9]
*ESR1*m	*21*	**8.3** [3.5-12.9]
*ESR1*wt	*27*	**9.0** [4.2-12.7]
*PIK3CA*m	*25*	**8.3** [3.6-10.2]
*PIK3CA*wt	*23*	**9.4** [4.0-NR]

- Ela/Eve
  - 72% visceral mets
  - 20% primary endocrine resistance
  - 100% prior CDK4/6i
    - 50% ribociclib
  - 70% one prior line of Rx
  - 50% prior fulvestrant
- Safety
  - Consistent with either everolimus + standard ET or elacestrant; no new safety signals observed
  - No bradycardia or photopsia
  - TEAE leading to elacestrant + everolimus drug withdrawal 6%
  - TEAE leading to elacestrant + everolimus drug dose reduction 2%

Rugo et al, SABCS 2025

Elevate (2)

- Ela/Abemaciclib
  - 92% visceral mets
  - 15% primary endocrine resistance
  - 50% prior CDK4/6i
  - 78% one prior line of Rx
  - 30% prior fulvestrant
- Safety
  - The safety profile is consistent with abemaciclib + standard ET or elacestrant; no new safety signals were observed
  - No bradycardia or photopsia
  - TEAE leading to elacestrant + abemaciclib drug withdrawal 0%
  - TEAE leading to elacestrant + abemaciclib drug reduction 5%

- **PFS: 14.3 months**
- 91.2% DCR
- 24.6% ORR
- 14.75 mos mDOR

	Elacestrant + abemaciclib	
Subgroup	**N**	**mPFS, months (95% CI)**
All patients	*60*	**14.3** [7.3-16.6]
Visceral disease	*55*	**14.3** [7.4-16.6]
No prior fulvestrant	*42*	**14.8** [8.7-NR]
No primary endocrine resistance	*51*	**14.3** [7.3-16.6]

Follow Up Time, median (95% CI), months: Overall: 8.6 (6.5-12.6) - Arm C: 5.7 (4.6-8.7) - Arm D: 11.6 (8.5-13.4)

Maturity not reached for PFS (95% CI) for genomic subgroups (*ESR1* / *PIK3CA*) or by prior CDK4/6i exposure

Arm C required prior CDK4/6i (palbociclib or ribociclib)
Arm D excluded prior CDK4/6i

EMBER-3: Imlunestrant as 2nd Line Therapy for HR+ MBC

ER+, HER2- ABC

Men and pre-[a]/post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[b]

R 1:1:1 N=874

- **Imlunestrant 400 mg QD** n=331 — **A**
- **SOC ET[c,d]** Fulvestrant or Exemestane n=330 — **B**
- **Imlunestrant 400 mg QD + abemaciclib[d]** n=213 — **C[e]**

88% fulvestrant

Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all patients[h]

Key Secondary Endpoints

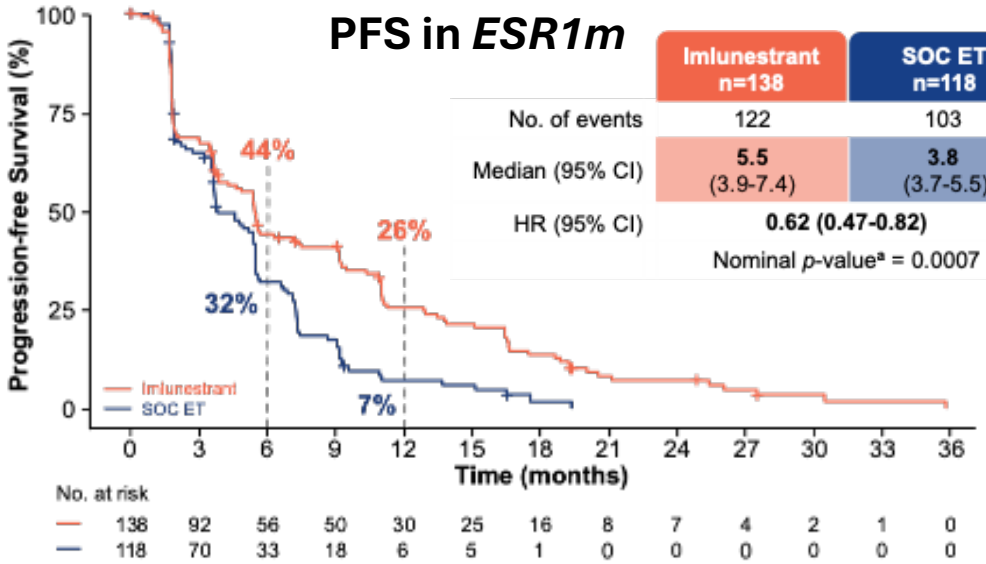
- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- TTC[i], CFS[j], PFS2[k]

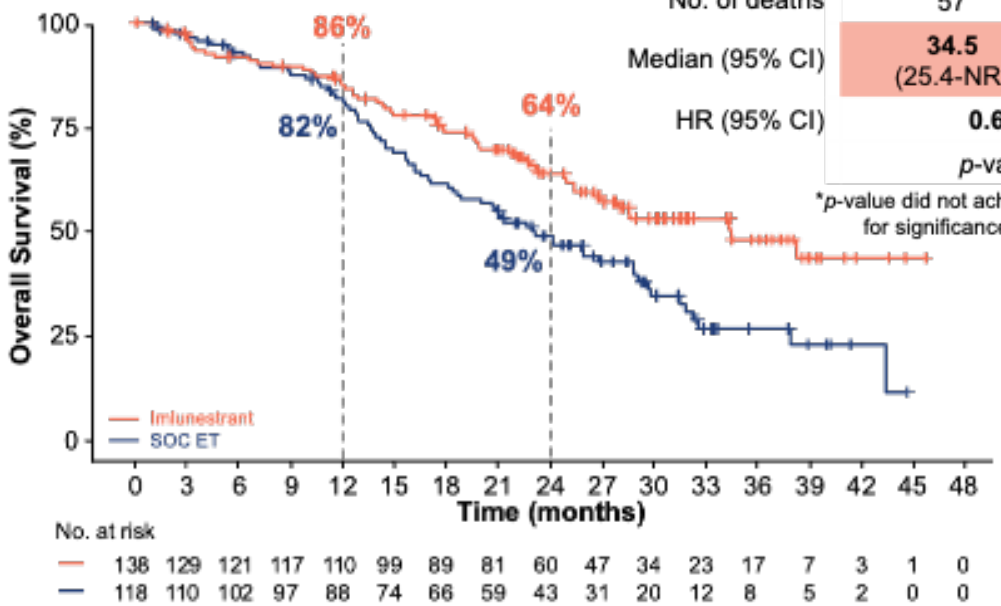
Median FU: 27.6 mo.

PFS in *ESR1m*



	Imlunestrant n=138	SOC ET n=118
No. of events	122	103
Median (95% CI)	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.47-0.82)**	
	Nominal *p*-value[a] = 0.0007	

Interim OS in *ESR1m* (50% maturity)



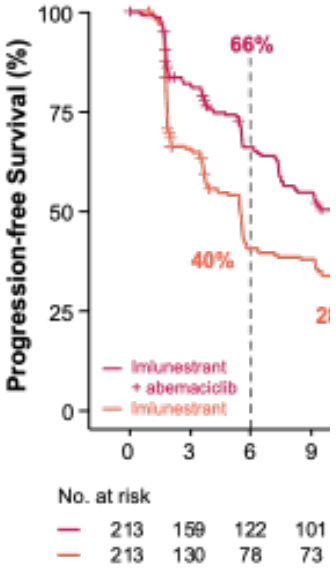
	Imlunestrant n=138	SOC ET n=118
No. of deaths	57	71
Median (95% CI)	**34.5** (25.4-NR)	**23.1** (18.4-28.9)
HR (95% CI)	**0.60 (0.43-0.86)**	
	p-value = 0.0043*	

*p-value did not achieve prespecified threshold for significance (*p*=0.0000004 at IA2)

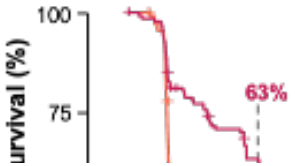
Jhaveri et al, NEJM 2025; Jhaveri et al, SABCS 2025

Imlunestrant/Abemaciclib vs Imlunestrant

PFS in all patients



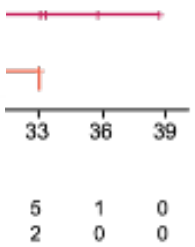
	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	144	174
	10.9	5.6



Prior CDK4/6i

	Imlunestrant + abemaciclib n=139	Imlunestrant n=140
No. of events	97	120
Median (95% CI)	9.1 (7.2-11.3)	3.7 (2.1-5.5)
	0.53 (0.40-0.69)	
	Nominal *p*-value < 0.0001	

EMBER-4: a randomized, open-label, global, multicenter, phase 3 adjuvant study (NCT05514054)



ER+, HER2- EBC

- Received 2-5 years of adjuvant ET ± **CDK4/6 inhibitor**
- Increased risk of recurrence

R 1:1 N=8,000

- Imlunestrant 400 mg daily
- Standard Adjuvant ET AI or Tamoxifen

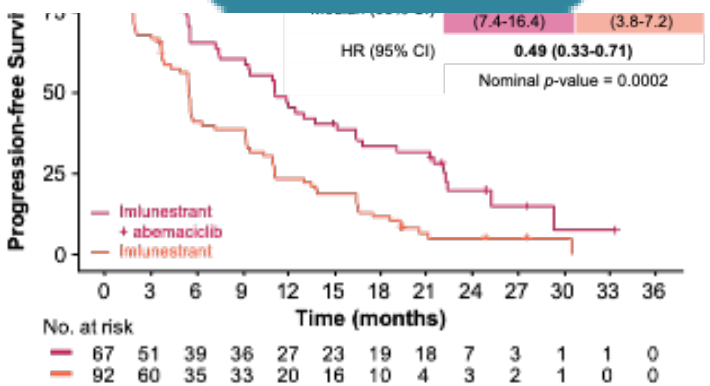
Stratification Factors

- Time from initial adjuvant ET
- Prior adjuvant CDK4/6i treatment
- Nodal status
- Menopausal status
- Geographic region

65 v 59% had pr

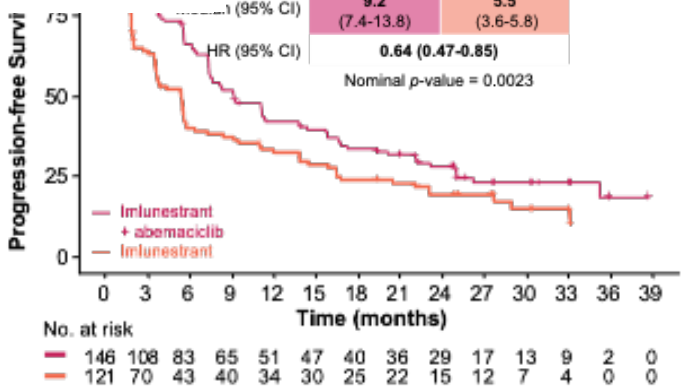
Benefit across PI3K pathway mutations

- Mutation
  - 7.6 v 3.8 mo (n=88 v 84, HR 0.57)
- No mutation
  - 11.3 v 5.6 mo (n=109 v 112, HR 0.59)



ts Without *ESR1*m

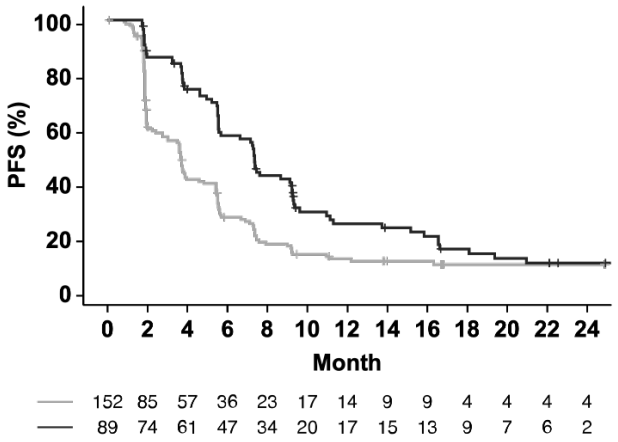
	Imlunestrant + abemaciclib n=146	Imlunestrant n=121
. of events	96	92
(95% CI)	9.2 (7.4-13.8)	5.5 (3.6-5.8)
HR (95% CI)	0.64 (0.47-0.85)	
	Nominal *p*-value = 0.0023	



Molecular Response Associated with Longer PFS in all Arms: Baseline to Week 4

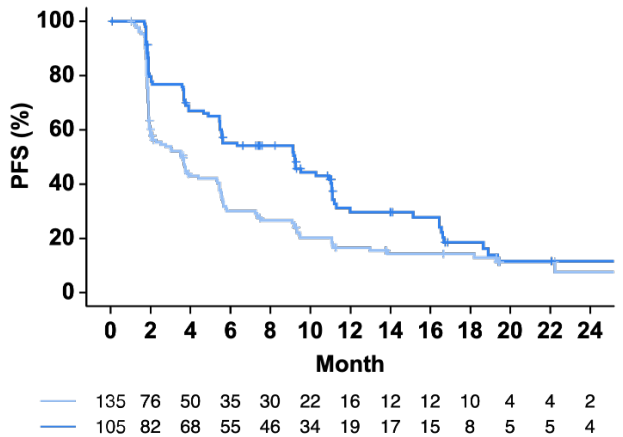
SOC ET (n=241)

	No MR	MR
Events, n (%)	126 (82.9)	70 (78.7)
Median PFS, mo	3.7	7.4
HR (95% CI)	0.56 (0.41, 0.75)	



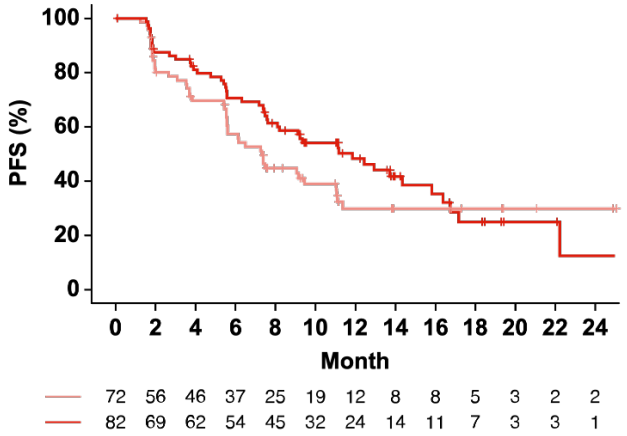
Imlunestrant (n=240)

	No MR	MR
Events, n (%)	108 (80.0)	76 (72.4)
Median PFS, mo	3.6	9.2
HR (95% CI)	0.62 (0.46, 0.83)	



Imlunestrant + abemaciclib (n=154)

	No MR	MR
Events, n (%)	44 (61.1)	47 (57.3)
Median PFS, mo	7.3	11.9
HR (95% CI)	0.75 (0.50, 1.14)	



CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; MR, molecular response; PFS, progression-free survival; SOC, standard of care.

- Early molecular response (decrease ≥50% in VAF of ctDNA at C2D1 vs. baseline predicts PFS but is this actionable?
  - Greatest decrease in the abemaciclib/imlunestrant arm
  - Does early change in therapy for lack of response change OS?

Bidard et al, SABCS 2025

evERA: Phase III Trial of Giredestrant plus Everolimus in HR+ MBC Post CDK4/6i

Key eligibility criteria*
- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET†
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

Enrollment period: August 2022 to October 2024

N = 373* → R 1:1

- Giredestrant (30 mg PO QD) + everolimus (10 mg PO QD)‡
- SOC ET§ + everolimus (10 mg PO QD)‡
  § Exemestane/fulvestrant/tamoxifen

Until PD or unacceptable toxicity

‡ Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

Co-primary endpoints (RECIST v1.1)
- INV-PFS in patients whose tumors had an *ESR1*m
- INV-PFS in the ITT population

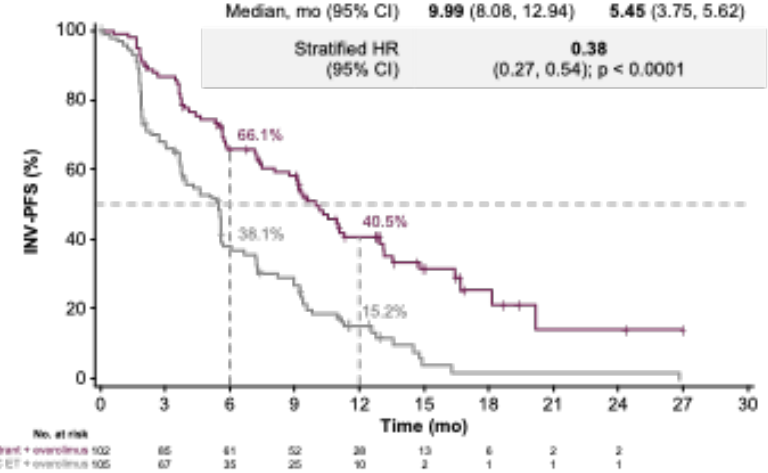
Key secondary endpoints
- OS
- INV-ORR, DoR

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumor DNA)
† Patients had to receive ≥ 6 months of CDK4/6i + ET in the aBC setting to be eligible for enrollment; prior fulvestrant was allowed

- Demographics
  - 47% prior fulvestrant
  - 25% CDK4/6i from 6 to 12 months
    - 57% v 63% palbociclib, even split with ribociclib and abemaciclib
  - Biomarkers
    - 55% ESR1 mutations
    - 35 vs 27% PIK3CA mutations
    - 45 vs 42% pathway alterations

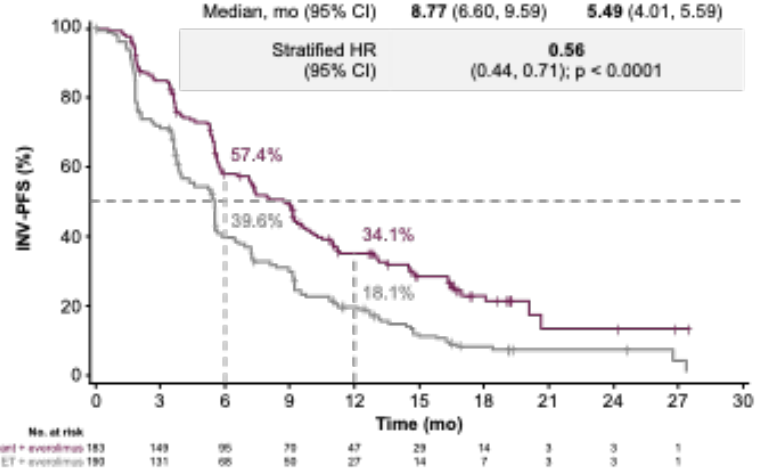
***ESR1*m**

	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	



ITT

	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	**8.77** (6.60, 9.59)	**5.49** (4.01, 5.59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); p < 0.0001	



Mayer et al, ESMO 2025; Rugo et al, SABCS 2025

Subset Analyses

- In both the ESR1m and ITT populations, the magnitude of clinical benefit was clinically meaningful and consistent, regardless of:
  - PIK3CAm and PIK3CA/AKT1/PTEN alterations
  - Duration of prior CDK4/6i
  - Choice of prior CDK4/6i (palbociclib, ribociclib, or abemaciclib)
- In secondary analysis, benefit for PFS appeared restricted to the altered population
- Safety as expected from each individual agent with low discontinuation rates

	Total, n	Patients, n: Giredestrant + everolimus	Patients, n: SOC ET + everolimus	HR (95% CI)
All patients with *ESR1*m[1]	207	102	105	0.42 (0.30, 0.59)
Genomic alteration				
*PIK3CA*m detected	64	35	29	0.38 (0.20, 0.69)
*PIK3CA*m not detected	143	67	76	0.47 (0.31, 0.70)
PIK3CA/AKT1/PTEN alteration detected	89	47	42	0.45 (0.27, 0.76)
PIK3CA/AKT1/PTEN alteration not detected	118	55	63	0.41 (0.26, 0.63)
All patients with *ESR1*m not detected	166	81	85	0.78 (0.56, 1.10)
Genomic alteration				
*PIK3CA*m detected	51	29	22	0.84 (0.47, 1.52)
*PIK3CA*m not detected	115	52	63	0.75 (0.50, 1.14)
PIK3CA/AKT1/PTEN alteration detected	73	35	38	0.69 (0.42, 1.14)
PIK3CA/AKT1/PTEN alteration not detected	93	46	47	0.89 (0.56, 1.41)
All ITT patients[1]	373	183	190	0.57 (0.45, 0.73)
Genomic alteration				
*PIK3CA*m detected	115	64	51	0.54 (0.36, 0.83)
*PIK3CA*m not detected	258	119	139	0.59 (0.45, 0.79)
PIK3CA/AKT1/PTEN alteration detected	162	82	80	0.54 (0.38, 0.77)
PIK3CA/AKT1/PTEN alteration not detected	211	101	110	0.60 (0.44, 0.83)

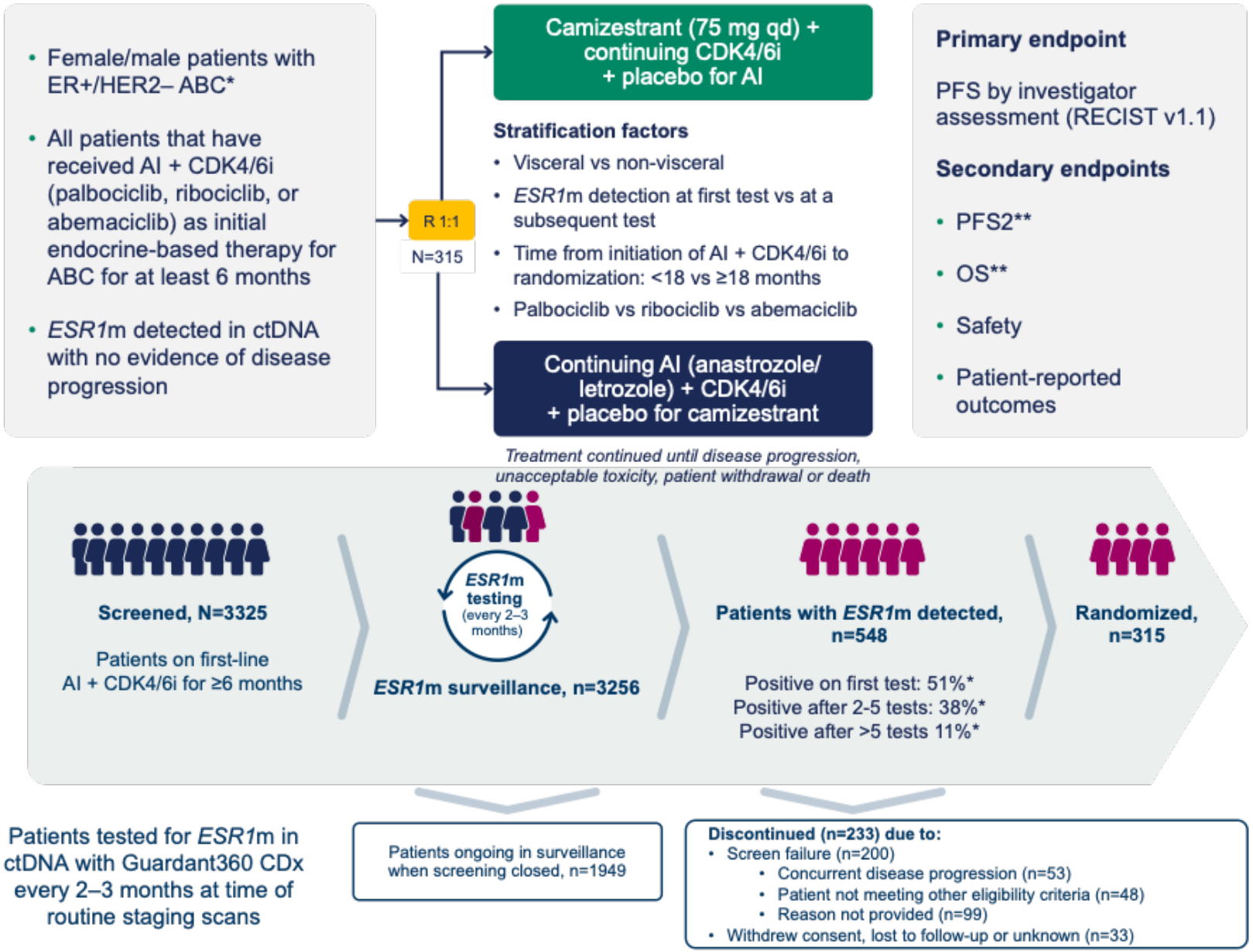
0.1 1.0

	*ESR1*m: Total, n	*ESR1*m: HR (95% CI)	*ESR1*m not detected: Total, n	*ESR1*m not detected: HR (95% CI)	ITT: Total, n	ITT: HR (95% CI)
All patients with *ESR1*m[1]	207	0.42 (0.30, 0.59)	166	0.78 (0.56, 1.10)	373	0.57 (0.45, 0.73)
Duration of prior CDK4/6i*						
< 12 mo	38	0.33 (0.16, 0.70)	56	0.84 (0.47, 1.50)	94	0.60 (0.38, 0.93)
12 to < 24 mo	74	0.42 (0.25, 0.73)	47	1.03 (0.54, 1.96)	121	0.66 (0.44, 0.99)
≥ 24 mo	92	0.39 (0.23, 0.66)	58	0.69 (0.38, 1.25)	150	0.50 (0.34, 0.75)
Prior CDK4/6i						
Palbociclib	126	0.40 (0.26, 0.61)	97	0.73 (0.46, 1.15)	223	0.53 (0.39, 0.73)
Ribociclib	66	0.71 (0.40, 1.26)	40	0.75 (0.38, 1.50)	106	0.75 (0.49, 1.16)
Abemaciclib	41	0.29 (0.14, 0.61)	61	1.12 (0.65, 1.95)	102	0.66 (0.43, 1.03)

0.1 1.0 2.0
Giredestrant + everolimus better
SOC ET + everolimus better

SERENA-6 Study Design and Disposition Over Time

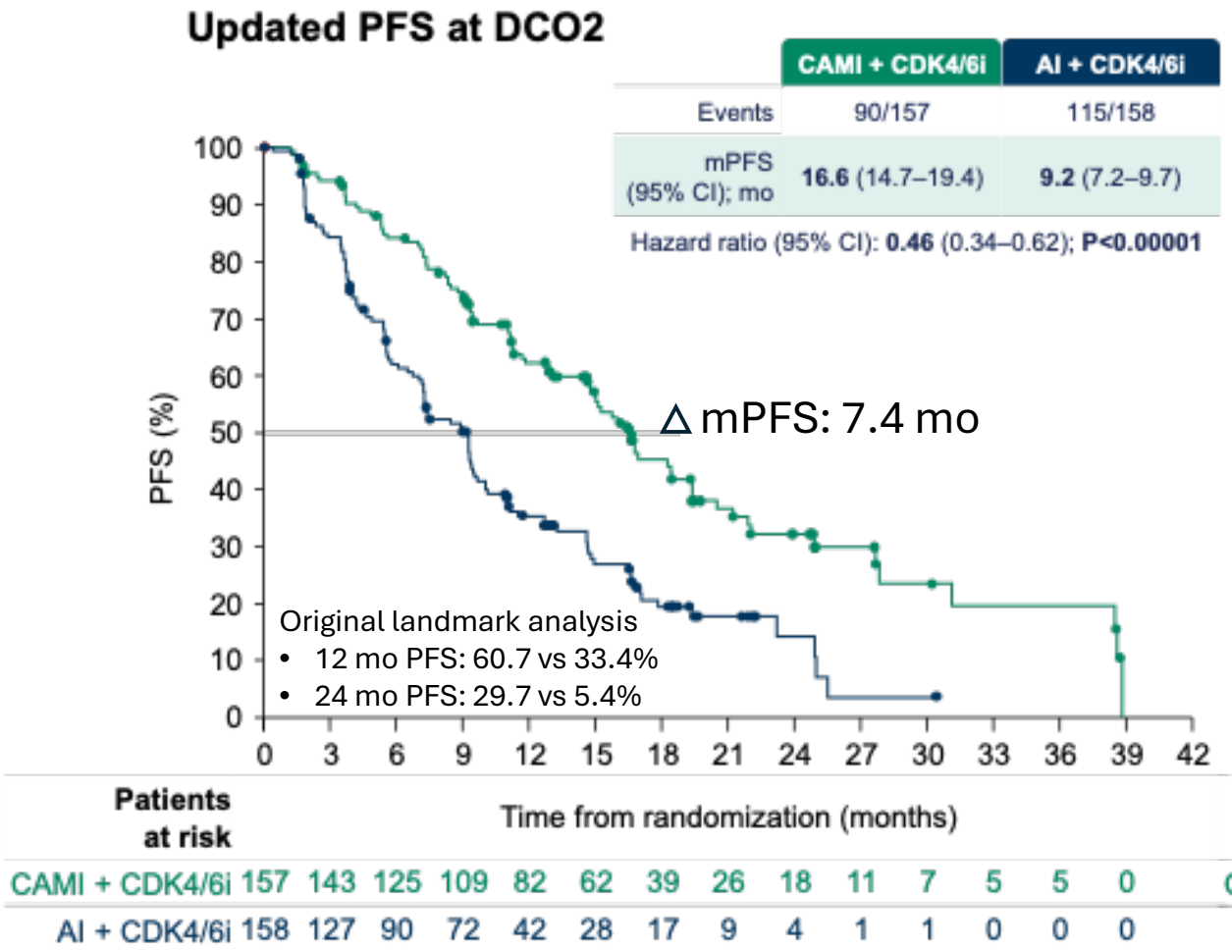
Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

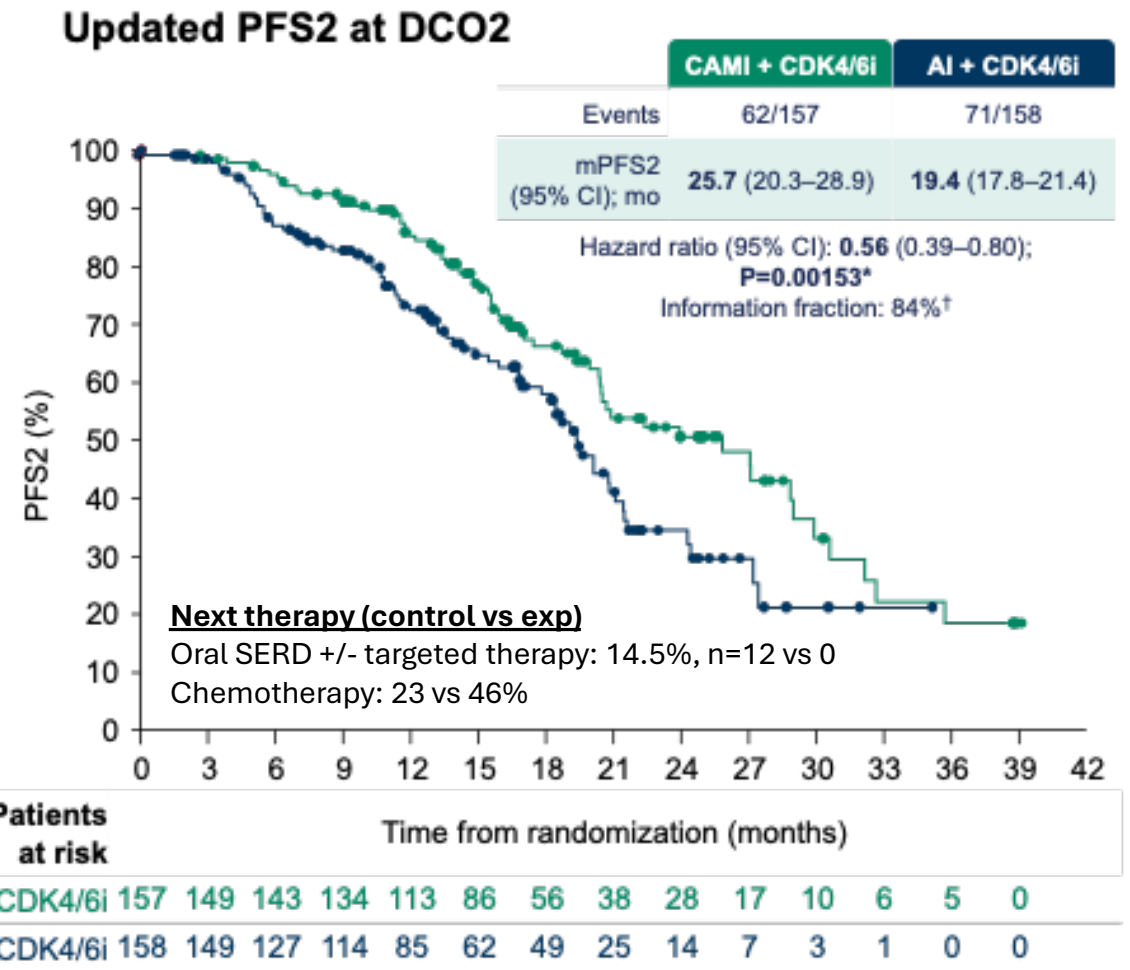


- ctDNA C1D1 and C3D1
- Median time to positive test when first test was positive: ~18 mo
- Median time to randomization: 23 mo
- 75-76% palbociclib

An estimate of the proportion of patients with emerging *ESR1*m during the study period is 42%, calculated from the 548 patients with a positive test/(the number of patients tested for *ESR1*m [n=3256] minus the number of patients that were **still ongoing in surveillance when screening closed [n=1949]).**

Turner N, ASCO 2025; Bidard FC, NEJM 2025



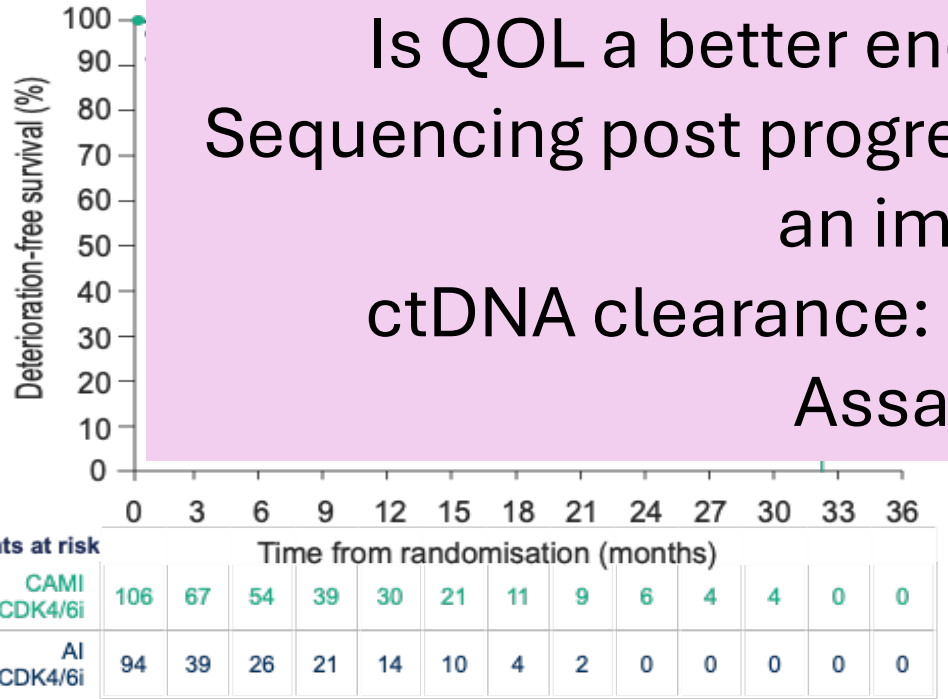


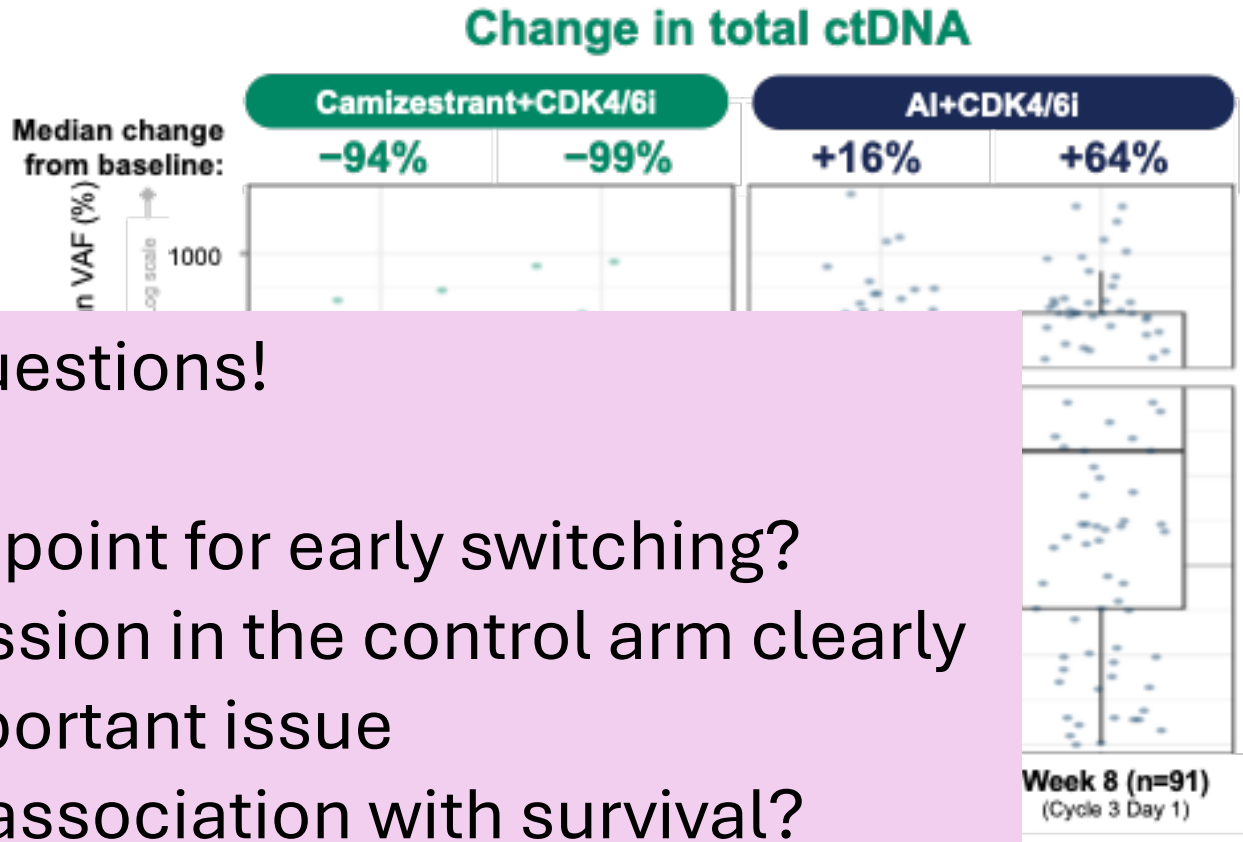
- Time to 1st subsequent therapy
  - HR: 0.47 (0.35–0.62)
- Time to 2nd subsequent therapy
  - HR: 0.57 (0.40–0.81)

Bidard et al, NEJM 2025 and SABCS 2025; Abstract RF7-03.

Serena-6: Additional Endpoints

Pain (
endp



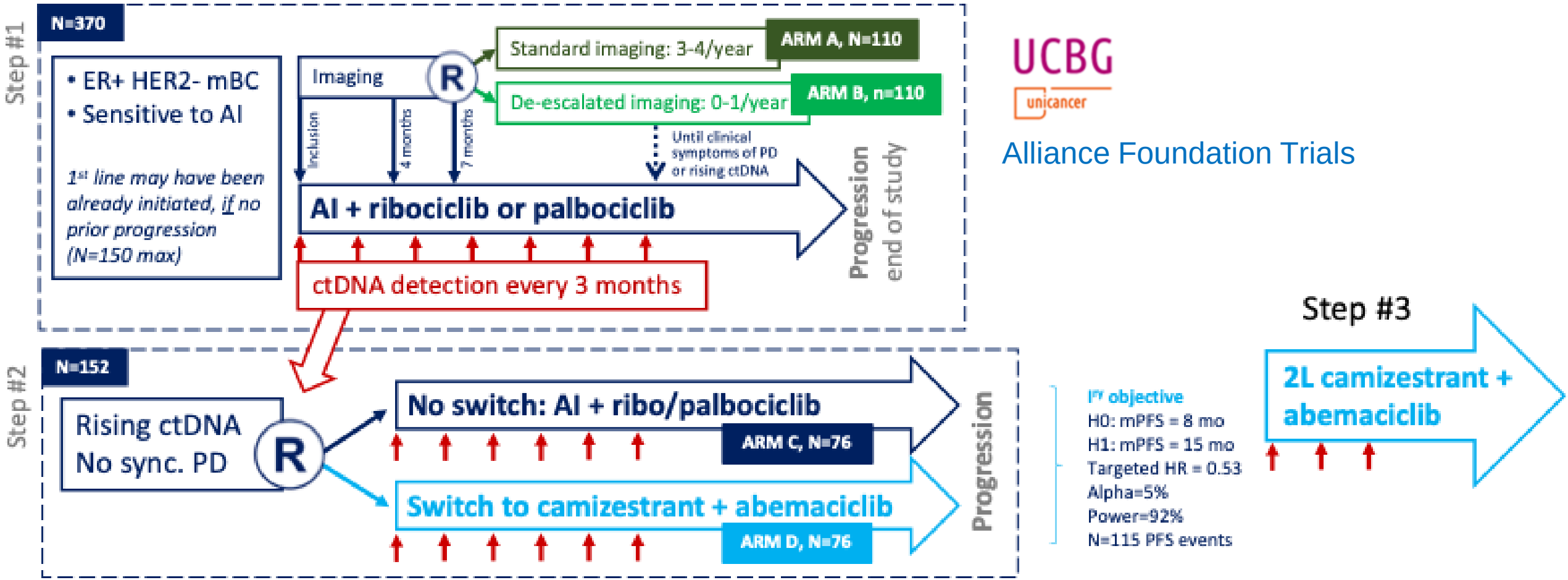


Questions!

Is QOL a better endpoint for early switching?
Sequencing post progression in the control arm clearly an important issue
ctDNA clearance: association with survival?
Assay sensitivity?

Bidard et al, ESMO BC 2025; Turner N, ASCO 2025; Bidard FC, NEJM 2025; Meyer et al, ESMO 2025; Bidard et al, ASCO 2026

Tailor Switch PADA-2



UCBG unicancer

Alliance Foundation Trials

PIs: Bidard and Rugo

VIKTORIA-1 (Phase 3): Gedatolisib + fulvestrant ± palbociclib vs fulvestrant for HR+, HER2–, PIK3CA WT advanced breast cancer

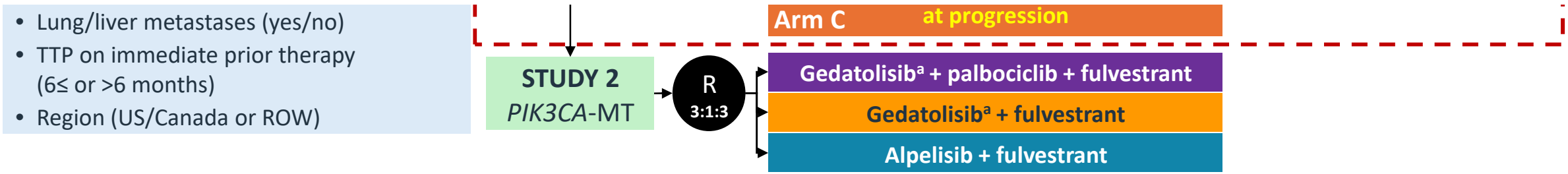
- Gedatolisib is a multitarget PAM inhibitor of all class I P13K isoforms, mTORC1 and mTORC2

Study 1 Efficacy:

- Gedatolisib + palbo + fulvestrant: mPFS 9.3 mo. (HR, 0.24; 95% CI, 0.17-0.35; P< 0.0001)
- Gedatolisib + fulvestrant: mPFS 7.4 mo. (HR, 0.33; 95% CI, 0.24-0.48; P< 0.0001)

Treatment-related AAs associated with gedatolisib:

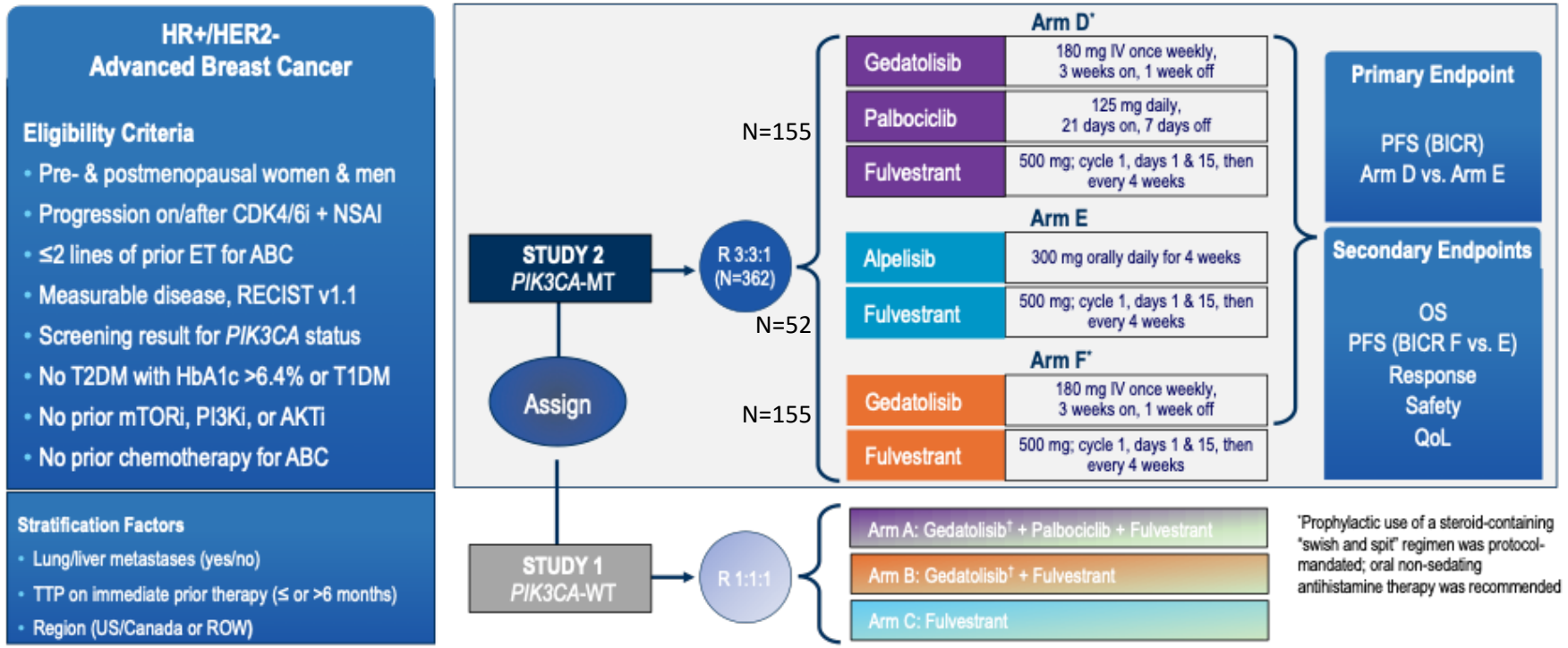
- Mainly grade 1-2
- Hyperglycemia and diarrhea were relatively uncommon
- Grade 3 stomatitis: triplet, 19.2%; doublet, 12.3%



[a]Prophylactic use of a steroid-containing "swish and spit" regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended.

Hurvitz SA, et al. JCO 2026; Pistilli et al, ESMO BC 2026

VIKTORIA-1: Study 2



Demographics

- 85-90% had 1 line of prior therapy
  - Median duration of prior CDK4/6i 17.5 – 22.1 mo
- 14-17% progressed <6 mo on last therapy
- ~44% de novo mBC; 75% visceral mets

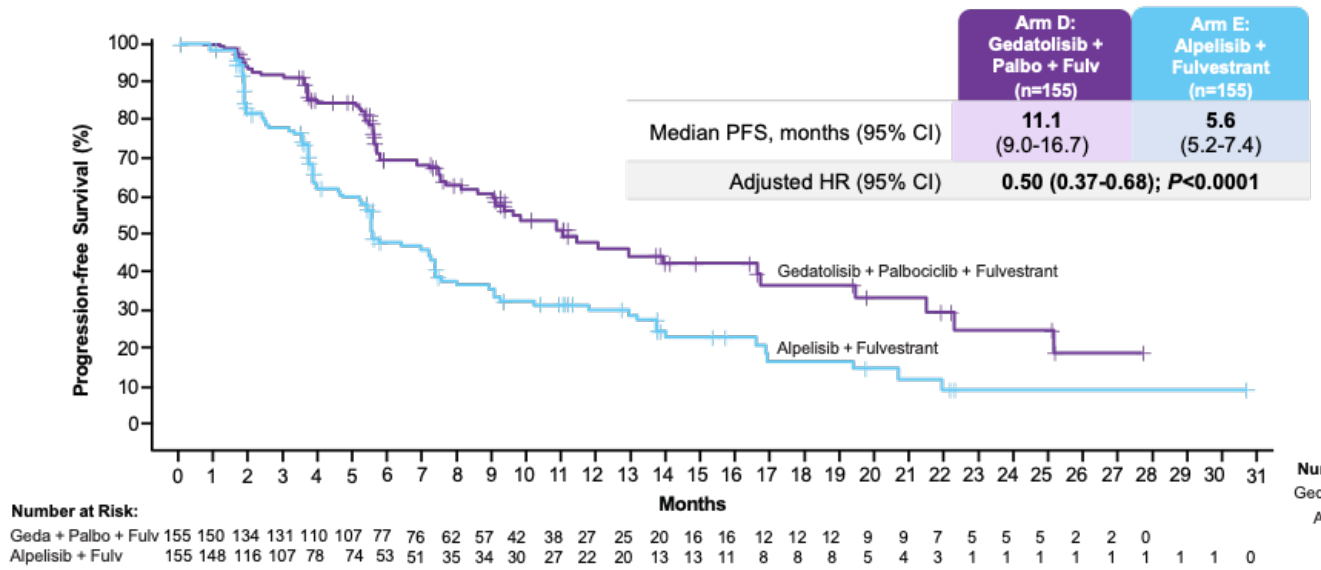
Safety (triple/doublet)

- Stomatitis
  - All grade stomatitis: 61-62%
  - Grade 3 stomatitis: 16.3/5.8%
- Other
  - Nausea 46/40%; grade 3 3/2%
  - Rash 26/33%; grade 3 ~6%

Hurvitz SA, et al. ASCO 2026

Primary Endpoint: Progression-Free Survival (BICR)

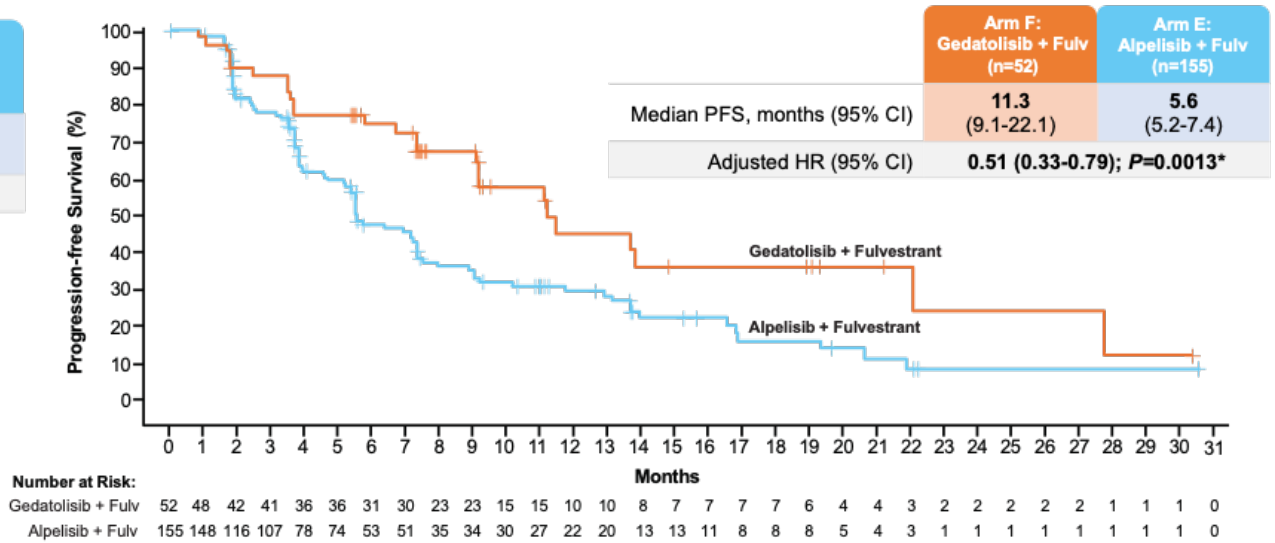
Gedatolisib Triplet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2



	Arm D: Gedatolisib + Palbo + Fulv (n=155)	Arm E: Alpelisib + Fulvestrant (n=155)
Median PFS, months (95% CI)	11.1 (9.0-16.7)	5.6 (5.2-7.4)
Adjusted HR (95% CI)	0.50 (0.37-0.68); *P*<0.0001	

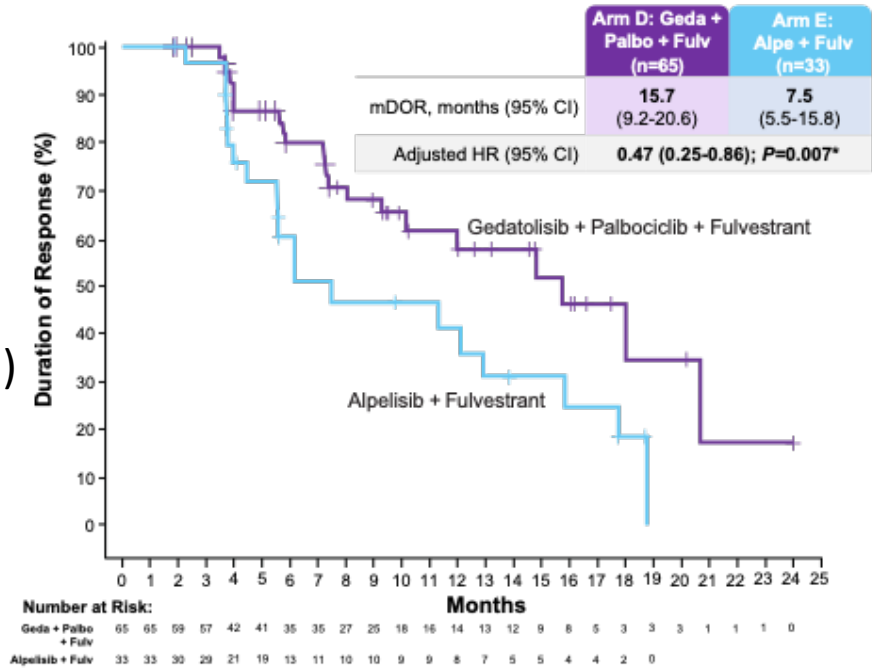
Secondary Endpoint: Progression-Free Survival (BICR)

Gedatolisib Doublet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2

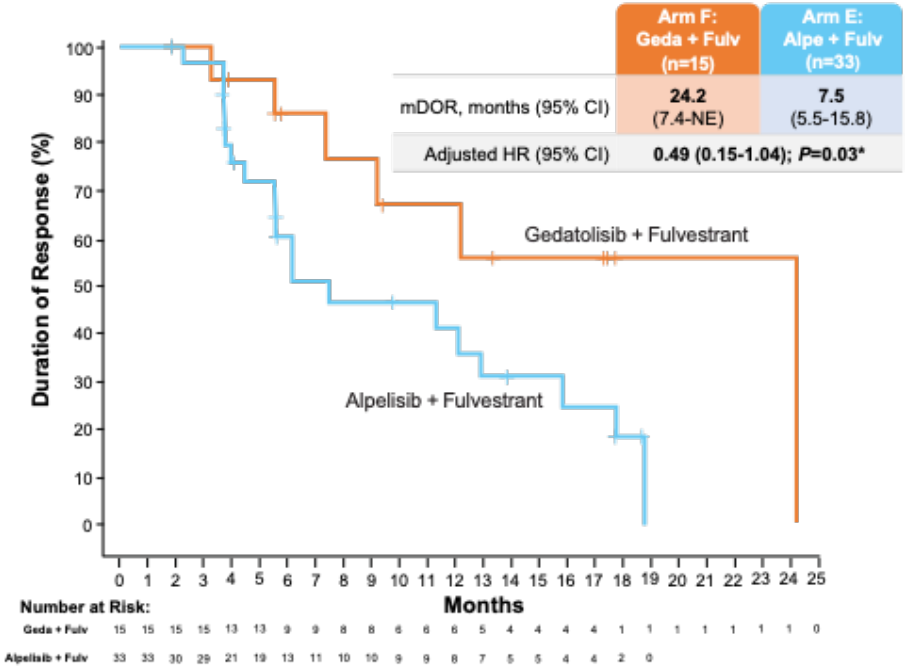


	Arm F: Gedatolisib + Fulv (n=52)	Arm E: Alpelisib + Fulv (n=155)
Median PFS, months (95% CI)	11.3 (9.1-22.1)	5.6 (5.2-7.4)
Adjusted HR (95% CI)	0.51 (0.33-0.79); *P*=0.0013*	

ORR:
49%, 36% and 26% (control)



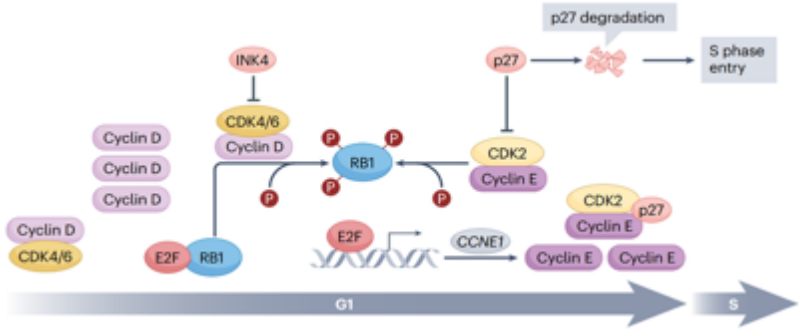
	Arm D: Geda + Palbo + Fulv (n=65)	Arm E: Alpe + Fulv (n=33)
mDOR, months (95% CI)	15.7 (9.2-20.6)	7.5 (5.5-15.8)
Adjusted HR (95% CI)	0.47 (0.25-0.86); *P*=0.007*	

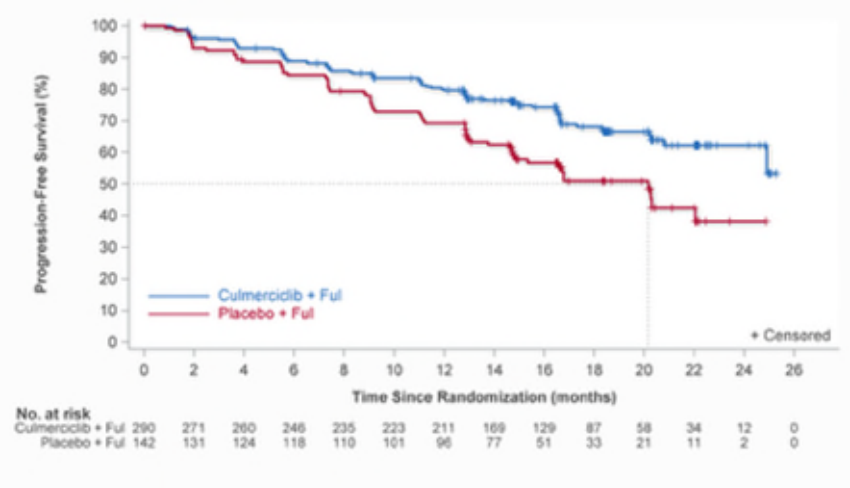


	Arm F: Geda + Fulv (n=15)	Arm E: Alpe + Fulv (n=33)
mDOR, months (95% CI)	24.2 (7.4-NE)	7.5 (5.5-15.8)
Adjusted HR (95% CI)	0.49 (0.15-1.04); *P*=0.03*	

New Directions: New Targets (examples)

- CDK 4, CDK 2, and CDK 2, 4, 6 inhibitors
  - CDK4i: atirmociclib
    - FourLight-3 (NCT06760637): 1st line phase III study accrual completed
    - FourLight-2: phase 2 second line; press release atirmo fulv superior to fulv alone
    - Efficacy in combination with vepedgestrant (ASCO 2026) and in triplet with zovegelasib in PIK3CA mutated tumors (press release)
  - CDK4i: BeOne BGB43395 Phase III Study
  - CDK 2, 4, 6 inhibitor: Culmerciclib (TQB3616)[1]:
    - Phase III 2nd line 2:1 with fulvestrant vs fulvestrant alone
      - One line prior ET or chemo, no prior CDK4/6i
      - N=293; PFS 16.6 months vs 7.5 months, HR 0.36, $P < 0.001$
    - Phase III 1st line 2:1 with fulvestrant vs fulvestrant alone
  - CDK 2, 4, 6 inhibitor: Phase Ib Moonrose trials (Roche/Genentech)
- KAT6i
  - Multiple trials from phase I to phase III





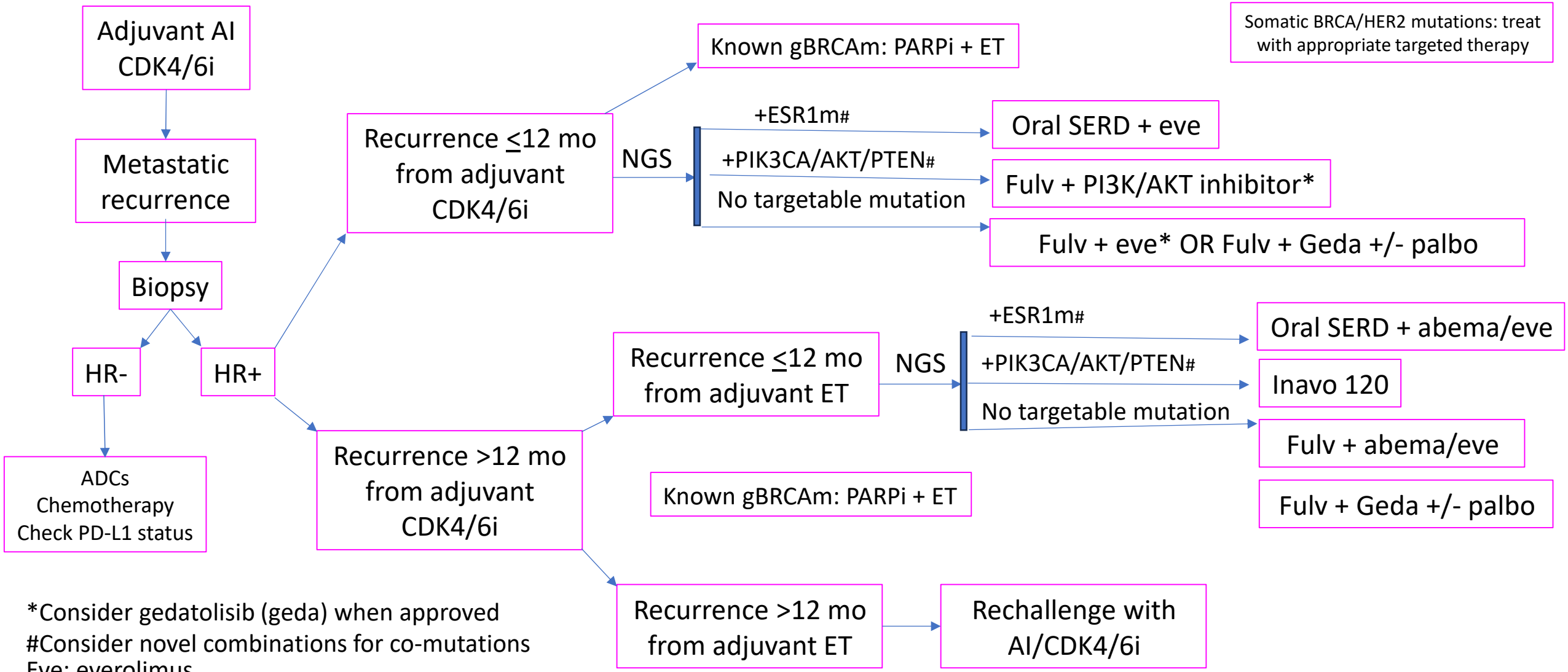
Treatment	Event / Total	Median (95% CI)
Culmerciclib + Fulvestrant	83 / 290	NR (24.9, NR)
Placebo + Fulvestrant	66 / 142	20.2 (14.8, NR)
HR=0.56 (95% CI 0.40, 0.78)*, *P=0.0004*		

1. Yin Y et al, Signal Transduction and Ther; 2025; Song et al, ESMO 2025

Next Steps in Targeting the PI3K/AKT/mTOR Pathway

- **Targeting PIK3CA with triplet therapy**
  - **Endocrine sensitive disease in the 1st line setting:**
    - INAVO123 (invavolisib, NCT06790693)
    - VIKTORIA-2 (gedatolisib, NCT06757634)
    - PIKALO-2 (tersolisib, NCT07174336)
  - **Endocrine resistant disease in the 1st line setting:**
    - CAPItello-292 (capivasertib, NCT04862663)
    - VIKTORIA-2 (gedatolisib, NCT06757634)
    - PIKALO-2 (tersolisib; NCT07174336)
- **Targeting PIK3CA in the >1st line setting**
  - ReDiscover 2
    - RLY-2608-102 (zovegalisib; NCT06982521)

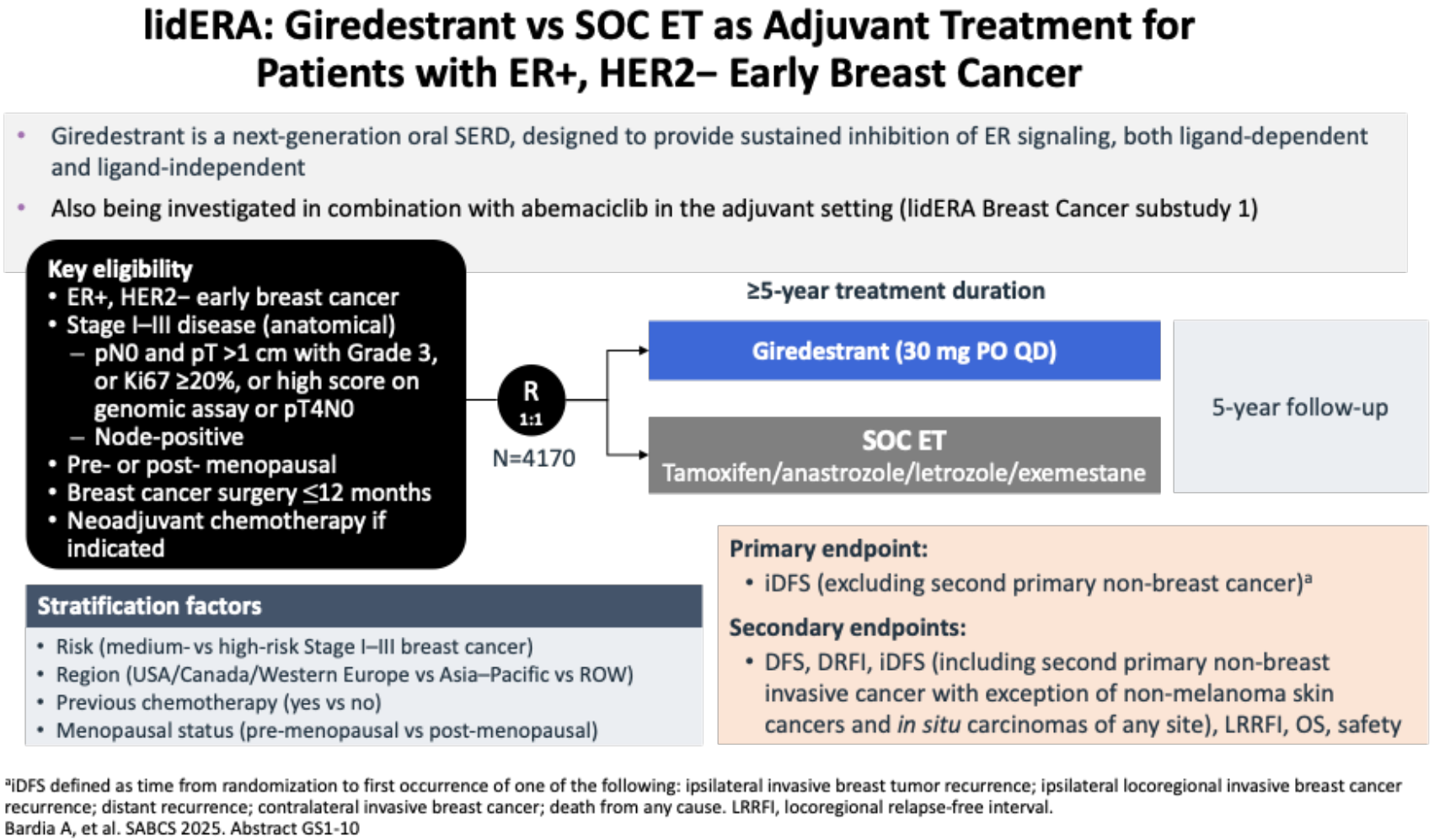
HR+/HER2- MBC: General Approach Post CDK4/6 Inhibitors



*Consider gedatolisib (geda) when approved
#Consider novel combinations for co-mutations
Eve: everolimus

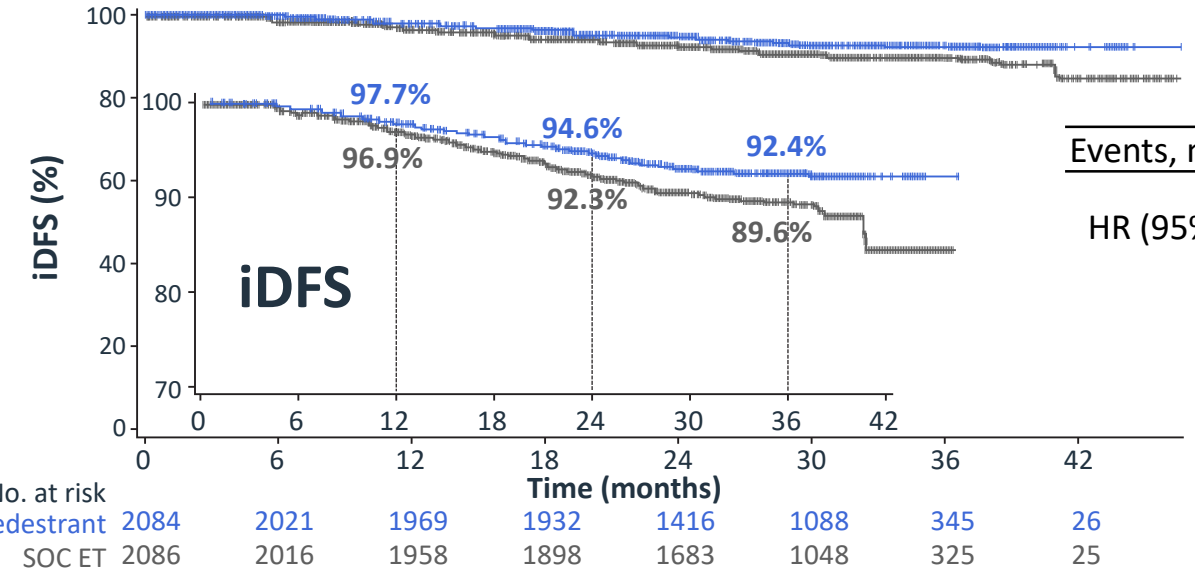
High Risk Early Stage HR+/HER2- Breast Cancer

- CDK 4/6 inhibition is now the standard of care with ET
- Can new endocrine agents further change outcome?



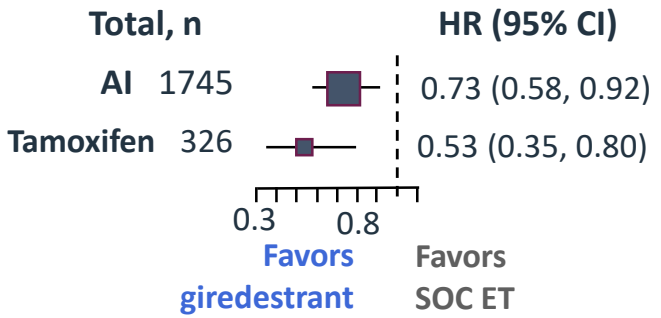
[a]iDFS defined as time from randomization to first occurrence of one of the following: ipsilateral invasive breast tumor recurrence; ipsilateral locoregional invasive breast cancer recurrence; distant recurrence; contralateral invasive breast cancer; death from any cause. LRRFI, locoregional relapse-free interval.
Bardia A, et al. SABCS 2025. Abstract GS1-10

lidERA iDFS: Median FU 32.3 months



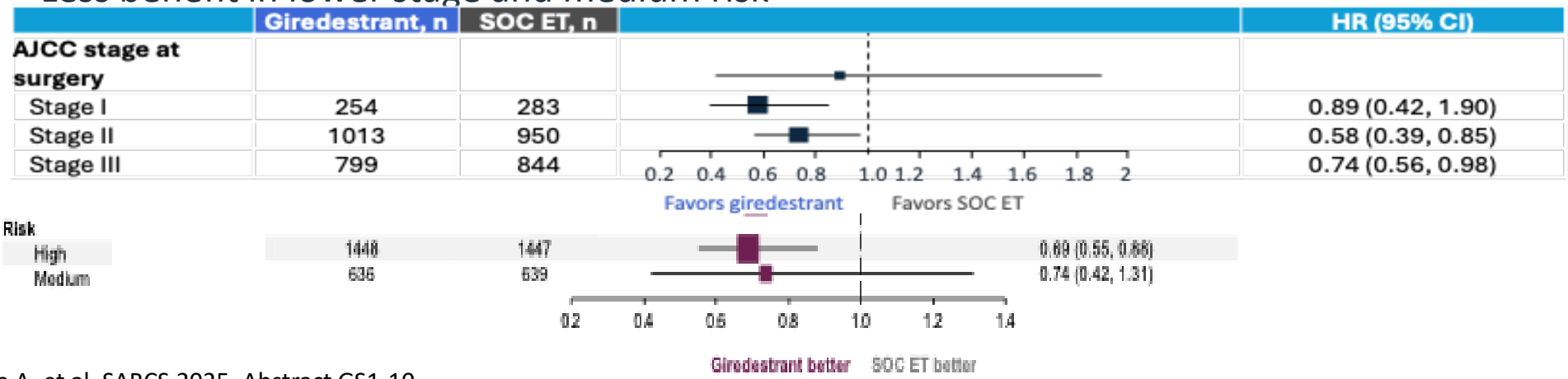
	SOC ET (n=2086)	Giredestrant (n=2084)
Events, n (%)	196 (9.4)	140 (6.7)
HR (95% CI)	0.70 (0.57, 0.87); P=0.014	

Exploratory analysis: iDFS by SOC ET



iDFS benefit was consistent across key prespecified subgroups

- Less benefit in lower stage and medium risk



Bardia A, et al. SABCS 2025. Abstract GS1-10

Median follow-up: 32.3 months; data cutoff: Aug 8, 2025

Oral SERDS: Ongoing Trials in the Adjuvant Setting

	SERD			
	Giredestrant	**Camizestrant**	**Imlunestrant**	Elacestrant
EARLY-STAGE SETTING				
Adjuvant setting (upfront)	**lidERA** NCT04961996 (**Phase 3**)	**CAMBRIA-2** NCT05952557 (Phase 3)		
Adjuvant setting (switch)		CAMBRIA-1 NCT05774951 **(Phase 3)**	**EMBER 4:** NCT05514054 (**Phase 3**)	**ELEGANT** NCT06492616 (Phase 3)

Results available

Trial completed accrual

New Directions

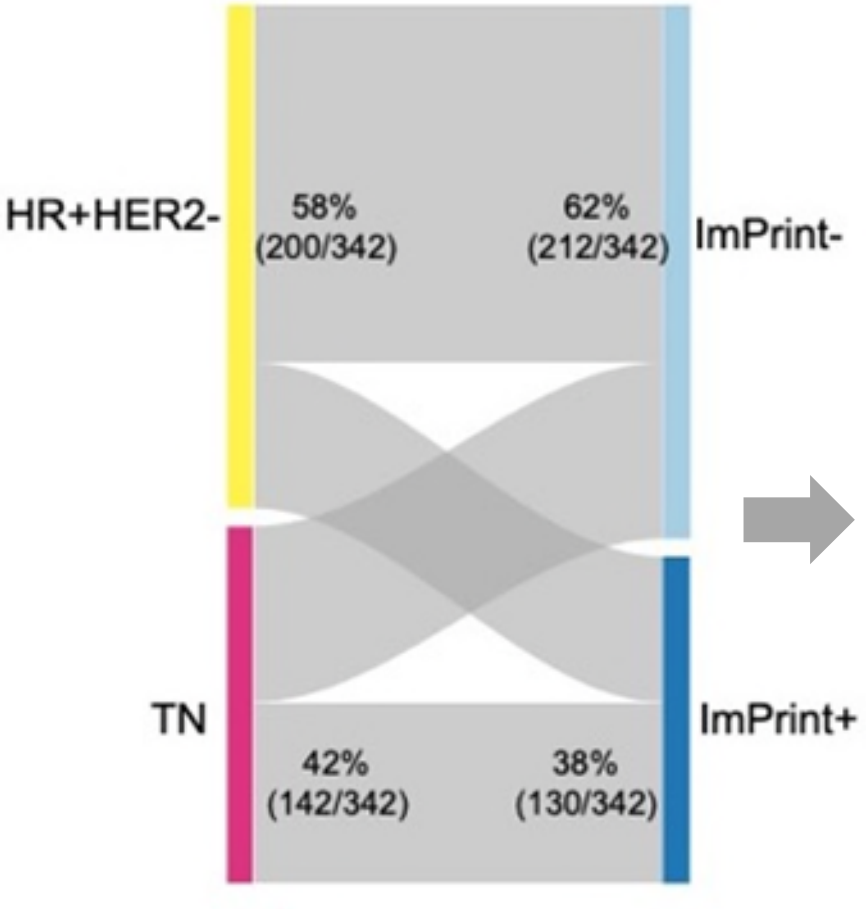
The I-SPY Example: Biomarkers to drive individualized treatment

I-SPY: Team-based science

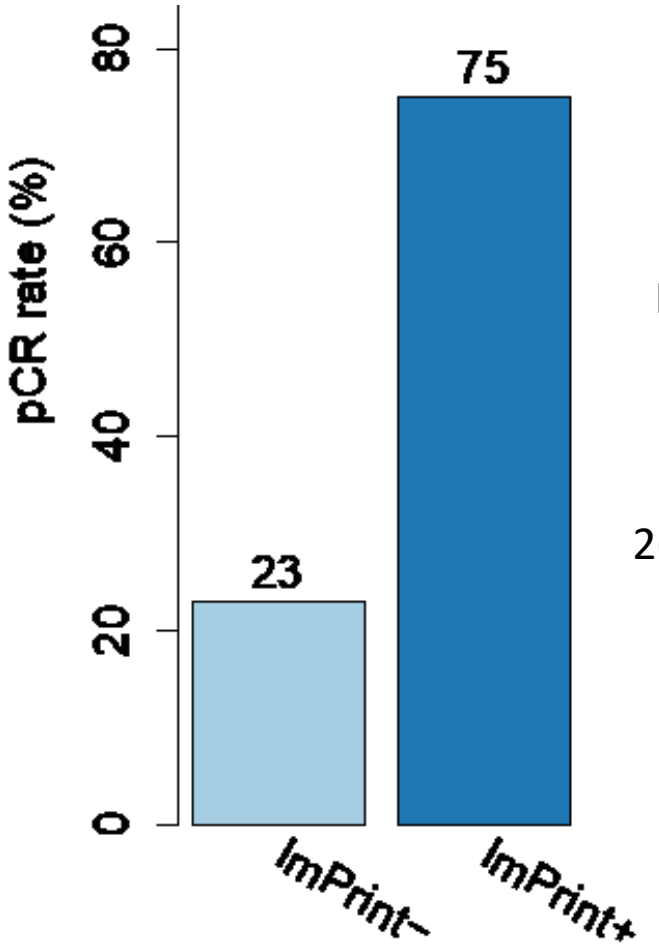
Working Groups

I-SPY2: Overall HER2- and HR+: IMPRINT Prevalence and Performance with Immunotherapy

(n=342 in 5 I0 arms) Now validated with datopotomab deruxtecan and dervalumab



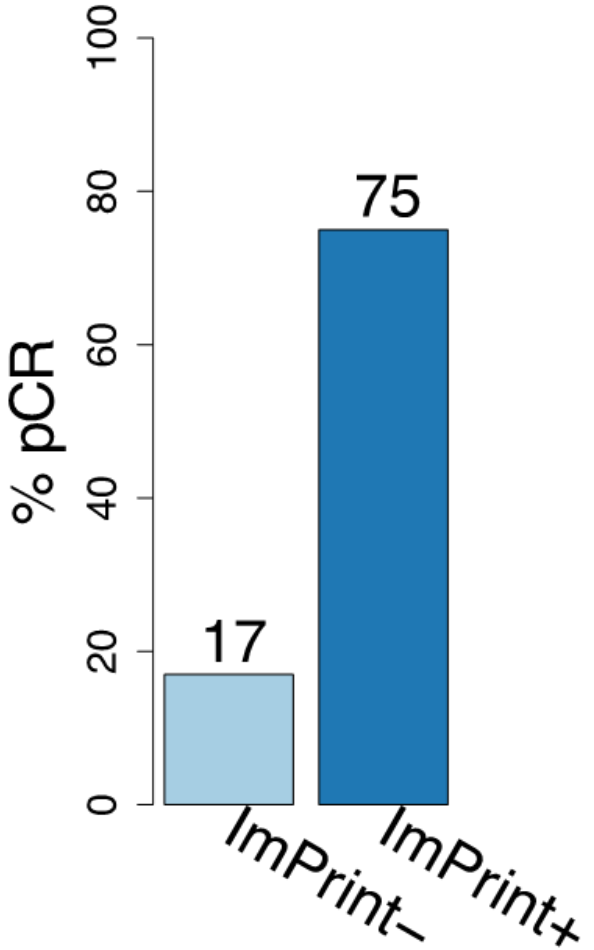
- *38% ImPrint+ overall*



- *75% pCR in ImPrint+*
- *23% pCR in ImPrint-*

HR+/HER2-
N=204

26% ImPRint+



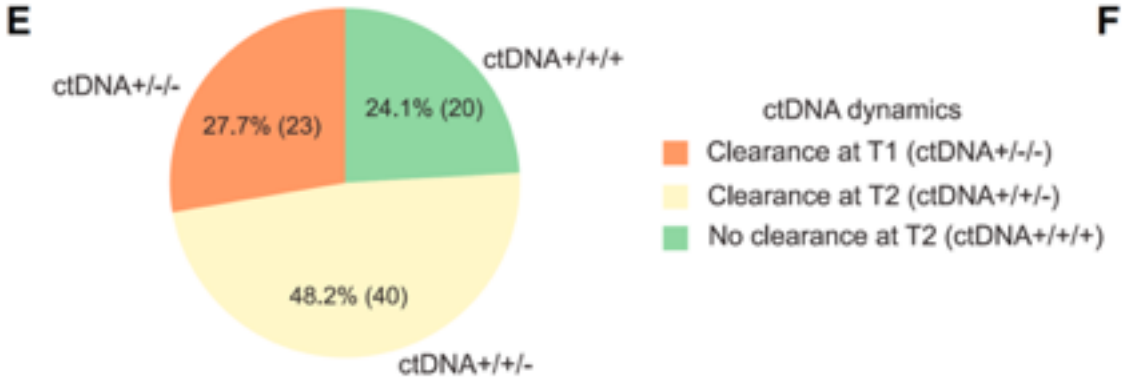
- *75% pCR in ImPrint+*
- *17% pCR in ImPrint-*

Wolf, Yau, et al, AACR 2024; Shatsky et al, Nat Med 2024

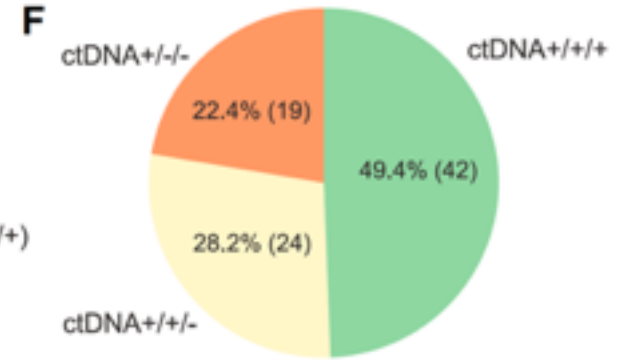
I-SPY2: ctDNA as a Biomarker of Response & Resistance for Early-Stage Disease Decrease During Treatment Predicts pCR

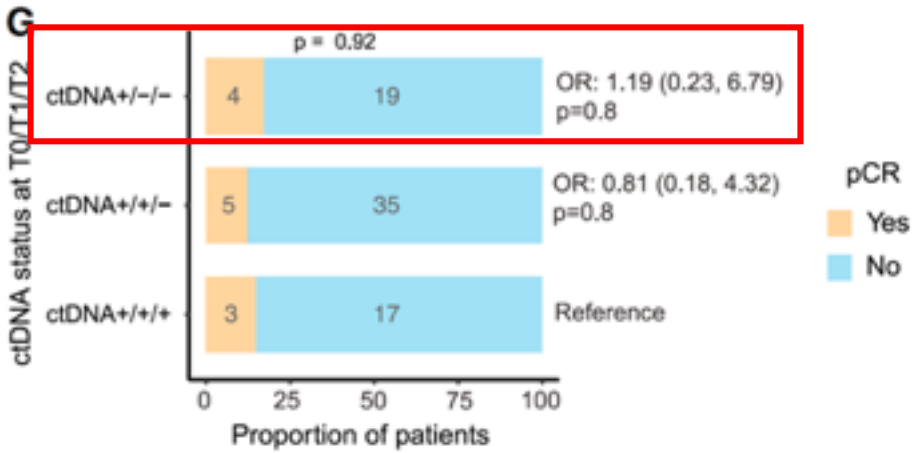
Compiled Series by Subtype

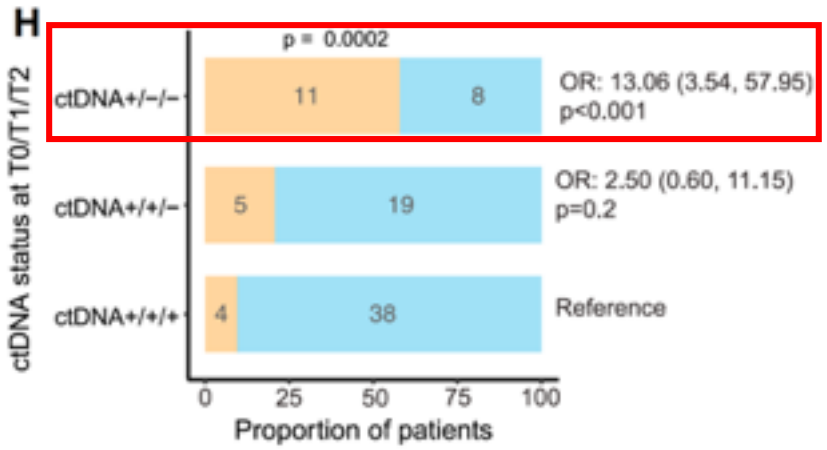
HR+/HER2-



Triple Negative







Early Clearance (T1) Strong Predictor of Response (pCR)

Magbanua et al, Cancer Cell, 2023
https://doi.org/10.1016/j.ccell.2023.04.008

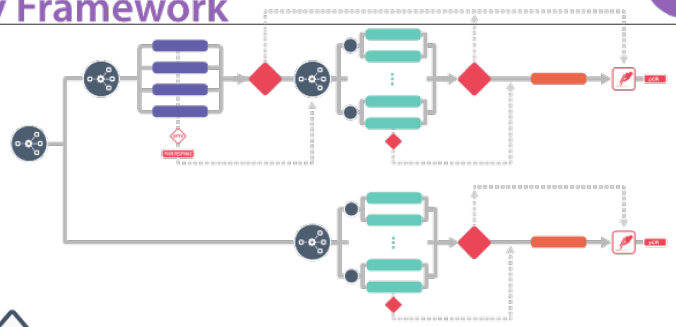
ROADMAP to Personalization

I-SPY 2.3

Optimize Strategy in a Regulatory Framework

- Randomization to contemporary control at second tx block
- Continue to optimize pCR by subtype
- Integrate PROs in trial and standard of care

GOAL: Minimize toxicity, increase chance of pCR and accelerated approval



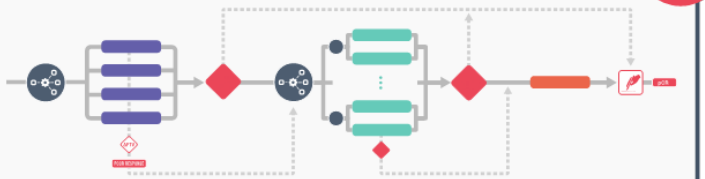
- Accelerated approval for agents with optimal pCR rates
- Introduce quantitative measures of toxicity
- Use combined endpoints for efficacy and toxicity
- Equal efficacy with less toxicity is superior

I-SPY 2.2

Adapt therapy within patients

- RCB, Imaging as a regulatory endpoint for poor & excellent responders ('preRCB')
- Allows early treatment switching and discontinuation depending on interim response to treatment

GOAL: Increase chance of pCR for each individual; reduce unnecessary toxicities



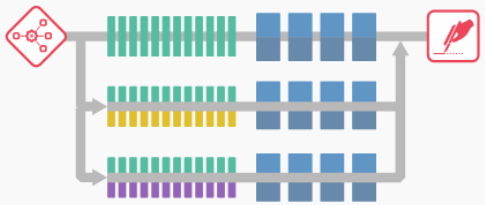
- Optimize pCR for each patient
- Stop at pCR, continue if not
- Confirm DRFS at 3 years ≥92% for pt with pCR

I-SPY 2

Adapt therapy within trial

- pCR regulatory endpoint (accelerated approval)
- Test multiple novel agents adaptively
- Operational efficiencies, platform trial, culture of innovation

GOAL: Increase pCR in each biomarker signature



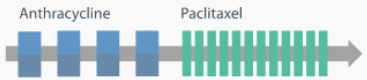
- pCR predicts DRFS HR 0.18 regardless of subtype, therapy
- RCB stratifies outcome
- Many agents identified that improve subtype specific pCR
- Molecular markers better classifiers than receptors

I-SPY 1

Measure outcomes by subtype

- Standardize imaging, pathology, biomarkers, data collection

GOAL: create collaborative framework & standards



- Absence of tumor after neoadjuvant chemo (pCR) is optimal early endpoint
- for molecularly high risk disease
- Better by subtype

“Somewhere, something incredible is waiting to be known.”
Carl Sagan

"If we knew what we were doing, it would not be called research, would it?”
Albert Einstein

Thank you!