National Comprehensive Cancer Network®

NCCN 2026 Breast Cancer Congress with Updates from the 2025 San Antonio Breast Cancer Symposium

Neoadjuvant/Adjuvant Treatment of Early-Stage Breast Cancer with SABCS Updates

Lisa E. Flaum, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Melissa M. McShane, MD
Fox Chase Cancer Center

Kay T. Yeung, MD, PhD
UC San Diego Moores Cancer Center

Early-Stage HER-2 Positive Breast Cancer

NCCN Breast Cancer Congress with SABCS Updates

February 13, 2026

Lisa E. Flaum, MD

Early-Stage HER2+ Breast Cancer

- Early-stage HER-2 positive breast cancer represents an evolving success story with many patients cured by combinations of chemotherapy and HER-2 targeted therapy
- Drug efficacy in the metastatic setting often leads to study and approval in early-stage disease
- For small/node negative HER-2 + tumors, primary surgery followed by adjuvant paclitaxel/traztuzumab is a standard of care based on data from the APT trial demonstrating excellent DFS rates
- For larger or node positive HER-2 + tumors, systemic therapy is typically recommended in the NA setting as pathologic response is prognostic and can guide adjuvant treatment decisions
- Meta-analyses demonstrate improved EFS and OS in patients with a pCR after NA therapy making it an in an important primary endpoint in NA studies
- Standard of care NA therapy includes taxane and/or anthracycline based regimens including TCHP or AC-TH (P) with pCR rates ranging from 40-68% (higher rates in ER negative disease)
- HER-2 directed therapy is continued in the adjuvant setting with TDM-1 the standard of care for patients who do not achieve a pCR

Tolaney, et al N Engl J Med 2015;372:134-141, Broglio, et al , JAMA Oncol. 2016;2(6):751. Cortazar, et al Lancet. 2014 Jul;384(9938), Schneeweiss, et al. Ann Oncol. 2013 Sep;24(9):2278-84

Early-Stage HER2 + Breast Cancer

- KATHERINE trial evaluated patients with residual disease after NA therapy, randomizing to traztuzumab vs TDM-1
  - 7 year IDFS: 67% with traztuzumab vs 80 % with TDM-1
  - 7 year OS: 84% with traztuzumab vs 89% with TDM-1
- Although all patients benefited from TDM-1, subset analyses demonstrated less favorable outcomes in certain patient populations.
  - Patients who were inoperable at time of surgery:
    - 7 year DFS 51% with traztuzumab vs 66% with TDM-1
  - Patients who were LN positive at time of surgery:
    - 7 year DFS 57% with trastuzumab vs 71% with TDM-1
  - Patients with HER-2 2+ FISH + disease had less favorable outcomes than those that were HER-2 3+
    - IHC 3+:7 year DFS 66% with traztuzumab vs 82% with TDM-1
    - IHC 2+: 7 year DFS 68% with traztuzumab vs 72% with TDM-1

Minckwitz, et al. N Engl J Med 2019;380:617-628, Geyer, et al. N Engl J Med 2025;392:249-25

Early-Stage HER-2 + Breast Cancer

- Other important caveats from the KATHERINE study
  - 70% of patients received anthracycline containing therapy in the NA setting
  - Only 20% of patients received dual HER-2 blockade in the NA setting
  - There was no improvement in brain mets as first site of recurrence with TDM-1
- While KATHERINE was practice changing, not all patient populations benefited equally, and outcomes remained poor in certain subsets representing an ongoing unmet need

Early-Stage HER-2 + Breast Cancer Questions/Challenges

- Can we escalate or de-escalate therapy in the adjuvant and neoadjuvant setting to improve outcomes, safety and tolerability?
- Can we improve outcomes for patients with residual disease after NA therapy, especially those with high-risk features and less favorable outcomes in the KATHERINE trial?
- Should we incorporate TDx-D, our most effective agent in the metastatic setting, in the early-stage setting?
    - Second line metastatic-DESTINY-Breast03: TDx-D improved median PFS to 28 months compared to 6.8 months with TDM-1
    - First line metastatic- DESTINY-Breast09: TDx-D plus pertuzumab improved median PFS to 40.7 months compared to 26.9 months with THP
- Can we use biomarkers to help predict pathologic response and outcomes and help tailor our treatment recommendations?

Cortes, et al N Engl J Med 2022;386:1143-1154, Tolaney, et al N Engl J Med. 2025

Early-Stage HER-2+ Disease SABCS Updates

- **Rapid Fire 6-01**: Interim analysis of DESTINY-Breast05
  - TDx-D vs TDM-1 in the HER-2 positive residual disease setting
- **Rapid Fire 6-02**: DESTINY-Breast11 safety analysis
  - TDx-D containing regimen vs standard of care in the NA HER-2 positive setting
- **GS1-06**: ctDNA in HER2+ Early Breast Cancer: Translational analysis of PHERGain neoadjuvant tailored treatment study

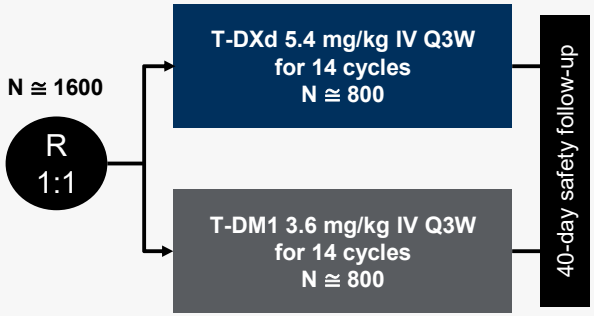
DESTINY-Breast05 study design

A global, multicenter, randomized, open-label, phase 3 trial (NCT04622319)

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[a]
- **High-risk defined as presentation prior to NAT with:**
  - **Inoperable eBC (cT4, N0-3,** M0 **or cT1-3, N2-3,** M0**) OR**
  - **Operable eBC (cT1-3, N0-1,** M0**) with axillary node–positive disease (ypN1-3) after NAT**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors
- Extent of disease at presentation (inoperable, operable)
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive, negative)



Primary endpoint
- IDFS

Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

- Concomitant adjuvant ET was allowed per local practices
- **If administered, RT could be initiated concurrently with study therapy or completed prior to initiation of study therapy (sequential) per investigator**

BMFI, brain metastasis–free interval; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; ypN, post-NAT pathologic nodal stage.
[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

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DB-05

Baseline demographics and clinical characteristics

	T-DXd n = 818	T-DM1 n = 817
Age, median (range), years	50.3 (24-78)	50.6 (21-83)
<65	735 (89.9)	736 (90.1)
≥65	83 (10.1)	81 (9.9)
Female sex, n (%)	814 (99.5)	814 (99.6)
Race		
White	301 (36.8)	333 (40.8)
Black or African American	22 (2.7)	13 (1.6)
Asian	**399 (48.8)**	**386 (47.2)**
Other	96 (11.7)	85 (10.4)
Region, n (%)		
Asia	**392 (47.9)**	**380 (46.5)**
Europe	222 (27.1)	223 (27.3)
North America + Australia	57 (7.0)	72 (8.8)
Rest of world[a]	147 (18.0)	142 (17.4)
ECOG PS score, n (%)		
0	656 (80.2)	652 (79.8)
1	162 (19.8)	165 (20.2)
HER2 expression,[b] n (%)		
IHC 3+	**676 (82.6)**	**670 (82.0)**
IHC 2+ and ISH+	129 (15.8)	133 (16.3)
IHC 2+ and ISH−	2 (0.2)	0
IHC 1+ and ISH+	11 (1.3)	14 (1.7)
Hormone receptor status,[c] n (%)		
Positive	**581 (71.0)**	**583 (71.4)**
Negative	237 (29.0)	234 (28.6)

	T-DXd n = 818	T-DM1 n = 817
Operative status at disease presentation,[c] n (%)		
Operable (cT1-3, N0-1, M0)	387 (47.3)	393 (48.1)
Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	**431 (52.7)**	**424 (51.9)**
Post-NAT pathologic nodal status,[c] n (%)		
Positive	**660 (80.7)**	**658 (80.5)**
Negative	158 (19.3)	159 (19.5)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	176 (21.5)	171 (20.9)
Trastuzumab + pertuzumab	**637 (77.9)**	**641 (78.5)**
Trastuzumab + other HER2-targeted therapy	3 (0.4)	3 (0.4)
Trastuzumab + pertuzumab + other HER2-targeted therapy	2 (0.2)	2 (0.2)
Neoadjuvant chemotherapy, n (%)		
Taxanes	818 (100)	817 (100)
Platinum compounds	386 (47.2)	392 (48.0)
Anthracycline	**423 (51.7)**	**399 (48.8)**
Radiotherapy treatment, n (%)		
Adjuvant radiotherapy	**764 (93.4)**	**759 (92.9)**
Concurrent	438 (53.5)	480 (58.8)
Sequential	326 (39.9)	279 (34.1)
No radiotherapy	54 (6.6)	58 (7.1)

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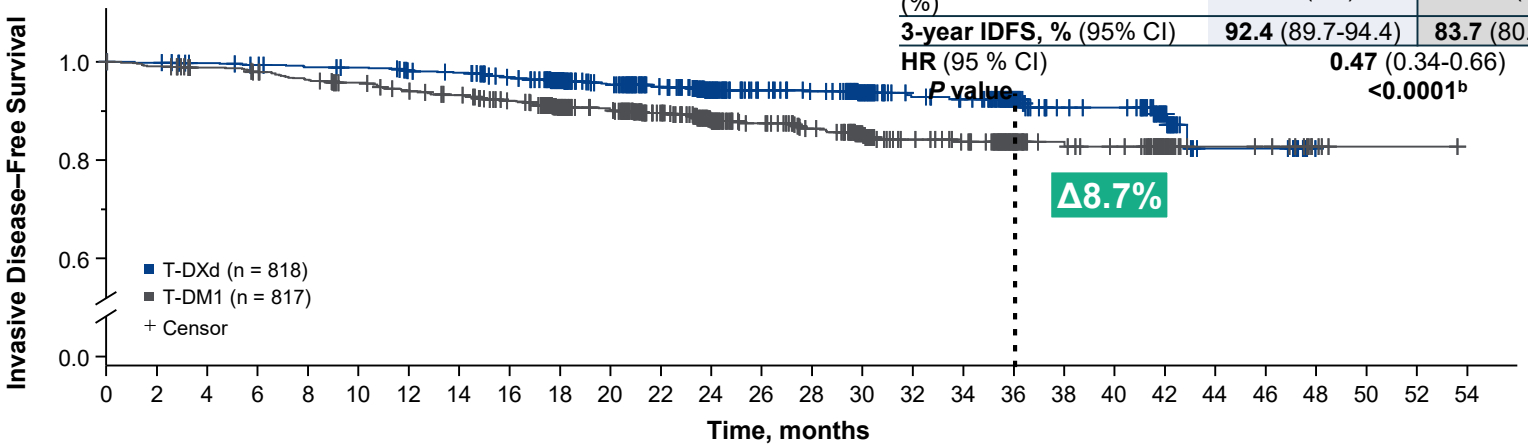
Primary endpoint: IDFS[a]

	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[b]**	



Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1

HR, hazard ratio; IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0183.
[a]IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. [b]Two-sided *P* value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

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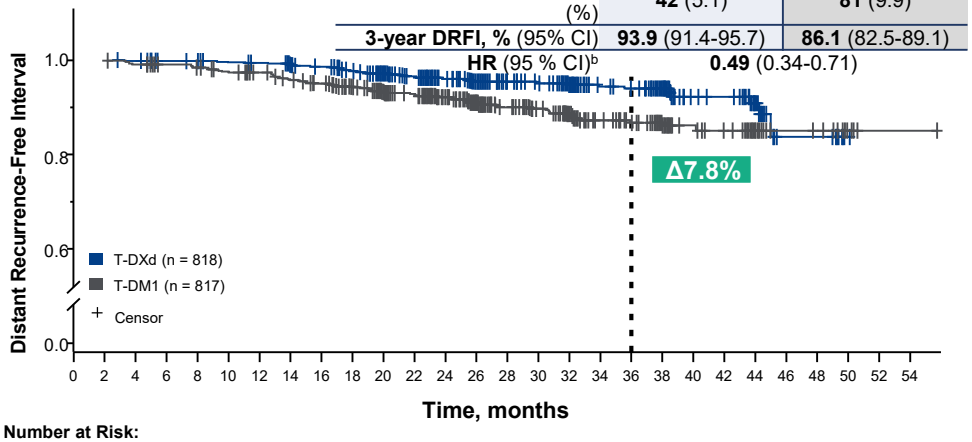
Secondary endpoints: DRFI[a], BMFI, and OS

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**42** (5.1)	**81** (9.9)
3-year DRFI, % (95% CI)	**93.9** (91.4-95.7)	**86.1** (82.5-89.1)
HR (95 % CI)[b]	**0.49** (0.34-0.71)	



Number at Risk:

T-DXd	818	786	778	774	770	767	757	753	731	684	635	545	442	382	372	276	219	213	129	92	90	46	14	14	0	0	0	0
T-DM1	817	780	769	761	746	739	724	713	694	639	606	533	424	362	345	240	192	182	121	84	79	38	14	13	4	1	1	0

	T-DXd n = 818	T-DM1 n = 817
BMFI		
Patients with recurrence in CNS, n (%)	**17** (2.1)	**26** (3.2)
3-year BMFI rate, % (95% CI)	**97.6** (96.2-98.5)	**95.8** (93.6-97.2)
HR (95% CI)[b]	**0.64** (0.35-1.17)	
OS (2.9% maturity)		
Patient deaths, n (%)	**18** (2.2)	**29** (3.5)
Survival at 3 years % (95% CI)	**97.4** (95.8-98.4)	**95.7** (93.5-97.2)
HR (95% CI)[b]	**0.61** (0.34-1.10)	

BMFI, brain metastasis–free interval; DRFI, distant recurrence–free interval; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]DRFI is defined as the time between randomization and the date of distant breast cancer recurrence. [b]HR and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

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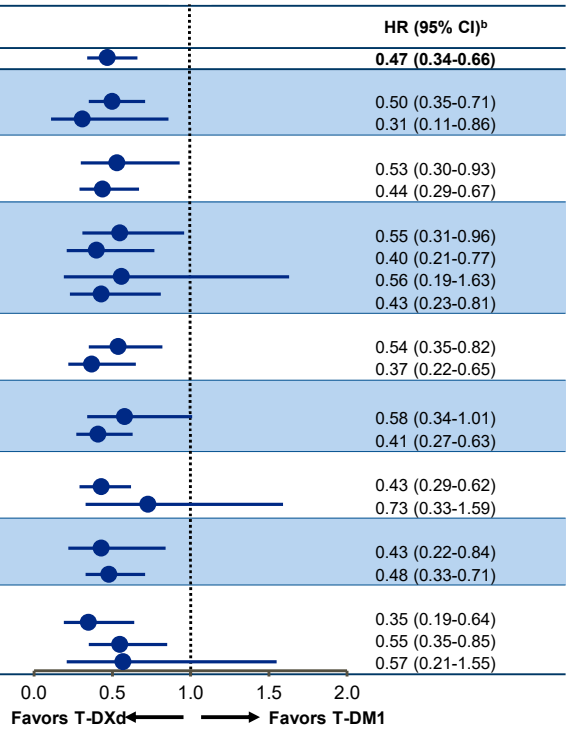
Primary endpoint subgroup analysis: IDFS

	No. events/patients		3-year IDFS, % (95% CI)		
	T-DXd	T-DM1	T-DXd n = 818	T-DM1 n = 817	HR (95% CI)[b]
All patients	**51/818**	**102/817**	**92.4 (89.7-94.4)**	**83.7 (80.2-86.7)**	**0.47 (0.34-0.66)**
Age					
<65 years	46/735	87/736	92.1 (89.2-94.3)	84.1 (80.2-87.2)	0.50 (0.35-0.71)
≥65 years	5/83	15/81	94.9 (87.0-98.1)	79.2 (67.9-87.0)	0.31 (0.11-0.86)
Race					
Asian	19/399	34/386	95.1 (91.9-97.0)	89.5 (85.3-92.6)	0.53 (0.30-0.93)
Non-Asian	32/419	68/431	89.5 (84.5-93.0)	77.9 (72.1-82.7)	0.44 (0.29-0.67)
Region					
Asia	19/392	33/380	95.0 (91.9-97.0)	89.7 (85.4-92.7)	0.55 (0.31-0.96)
Europe	13/222	30/223	93.1 (86.9-96.4)	82.9 (75.8-88.1)	0.40 (0.21-0.77)
North America + Australia	5/57	10/72	85.8 (63.9-94.9)	80.7 (65.3-89.7)	0.56 (0.19-1.63)
Rest of world	14/147	29/142	85.1 (73.6-91.8)	69.2 (56.3-79.0)	0.43 (0.23-0.81)
Hormone receptor status					
Postive	33/581	59/583	93.5 (90.6-95.6)	86.8 (82.9-89.9)	0.54 (0.35-0.82)
Negative	18/237	43/234	89.4 (82.0-93.9)	75.6 (67.6-81.9)	0.37 (0.22-0.65)
Disease status at presentation before NAT					
Operable (cT1-3, N0-1, M0)	21/387	34/393	92.8 (88.0-95.7)	88.4 (83.8-91.8)	0.58 (0.34-1.01)
Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	30/431	68/424	92.0 (88.5-94.5)	79.4 (73.9-83.8)	0.41 (0.27-0.63)
Post-NAT pathologic nodal status					
Positive[a]	40/660	87/658	92.5 (89.3-94.8)	82.5 (78.4-85.9)	0.43 (0.29-0.62)
Negative[a]	11/158	15/159	91.6 (85.3-95.3)	88.3 (80.6-93.0)	0.73 (0.33-1.59)
HER2-targeted NAT					
Single	13/176	27/171	87.5 (77.6-93.3)	77.9 (67.7-85.2)	0.43 (0.22-0.84)
Dual	38/642	75/646	93.6 (90.9-95.5)	85.2 (81.4-88.2)	0.48 (0.33-0.71)
Radiotherapy treatment					
Sequential radiotherapy	15/326	34/279	93.8 (88.4-96.7)	83.2 (76.4-88.2)	0.35 (0.19-0.64)
Concurrent radiotherapy	30/438	57/480	92.8 (89.7-95.0)	85.1 (80.6-88.6)	0.55 (0.35-0.85)
No radiotherapy	6/54	11/58	81.0 (61.0-91.4)	73.4 (56.4-84.6)	0.57 (0.21-1.55)



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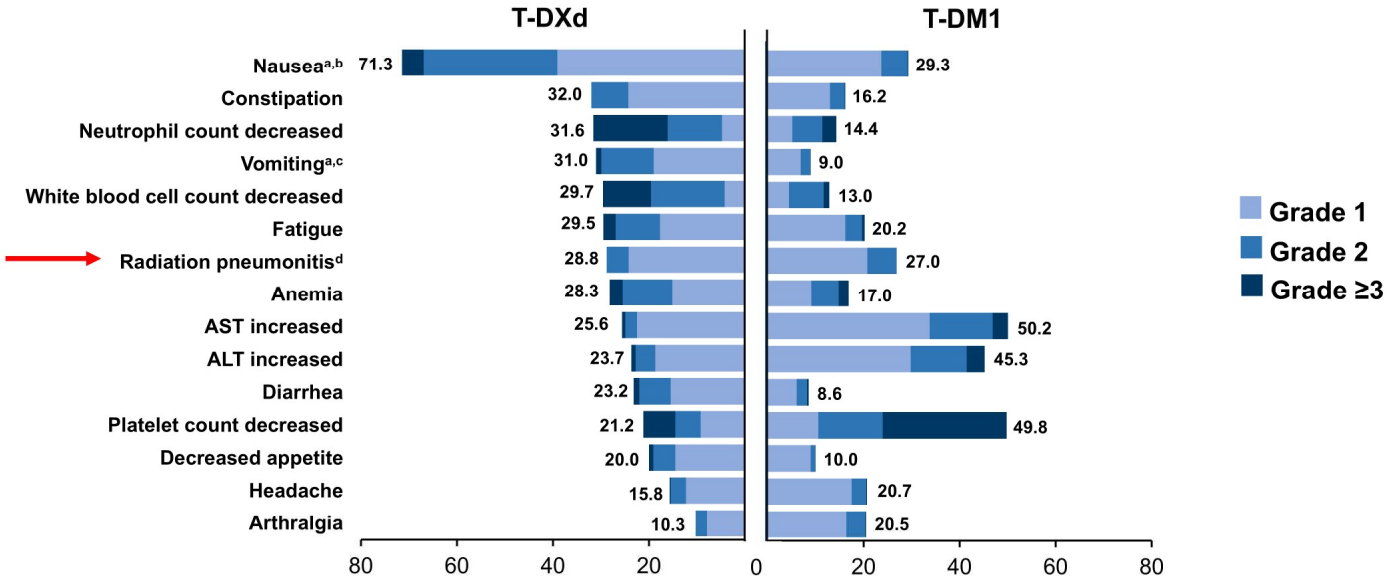
TEAEs in ≥20% of patients (either arm)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[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. [d]In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1, 4.6% and 6.1% grade 2 events.

Dr Charles E Geyer Jr

DESTINY-Breast05

BERLIN 2025 ESMO congress

Adverse events of special interest: ILD/pneumonitis and LV dysfunction

n (%)	Adjudicated Drug-related ILD					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	77 (9.6)	16 (2.0)	52 (6.5)	7 (0.9)	0	2 (0.2)
T-DM1 (n = 801)[a]	13 (1.6)	8 (1.0)	5 (0.6)	0	0	0

Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

Similar distributions of any grade adjudicated drug-related ILD events were observed with sequential and concurrent radiotherapy in both treatment arms (T-DXd: 10.7% and 9.6.% vs T-DM1: 2.6% and 1.0%, respectively)

n (%)	LV dysfunction					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	23 (2.9)	1 (0.1)	20 (2.5)	2 (0.2)	0	0
T-DM1 (n = 801)[a]	14 (1.7)	0	11 (1.4)	3 (0.4)	0	0

CT, computed tomography; ILD, interstitial lung disease; LV, left ventricular; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least 1 dose of study treatment.

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DECEMBER 9–12, 2025
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Additional efficacy and safety from the DESTINY-Breast05 study of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with high-risk human epidermal growth factor receptor 2–positive (HER2+) primary early breast cancer with residual invasive disease after neoadjuvant therapy

Sibylle Loibl,[1] **Yeon Hee Park, Zhiming Shao, Chiun-Sheng Huang, Carlos Barrios, Jame Abraham, Aleix Prat, Naoki Niikura, Michael Untch, Seock-Ah Im, Wei Li, Huiping Li, Yongsheng Wang, Herui Yao, Sung-Bae Kim, Elton Mathias, Jennifer Petschauer, Wenjing Lu, Hemali Upadhyaya, Charles E Geyer Jr**

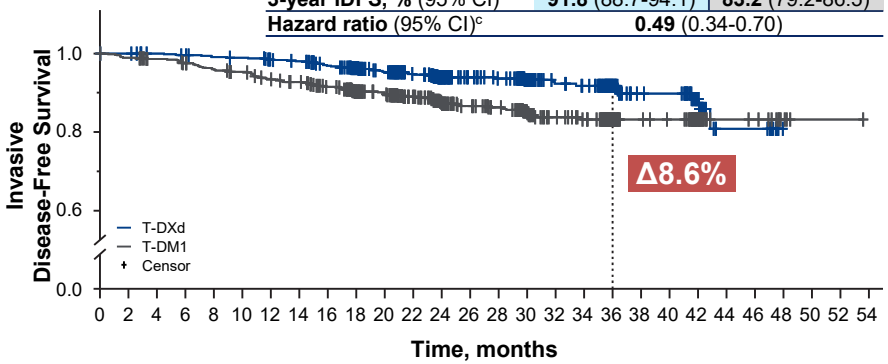
On behalf of the DESTINY-Breast05 investigators

RF6-01
Wednesday, December 10, 2025

IDFS subgroup analysis: HER2 status[a]

HER2 IHC 3+

	T-DXd n = 676	T-DM1 n = 670
Patients with events, n (%)	**46** (6.8)	**86** (12.8)
3-year IDFS, % (95% CI)	**91.8** (88.7-94.1)	**83.2** (79.2-86.5)
Hazard ratio (95% CI)[c]	**0.49** (0.34-0.70)	

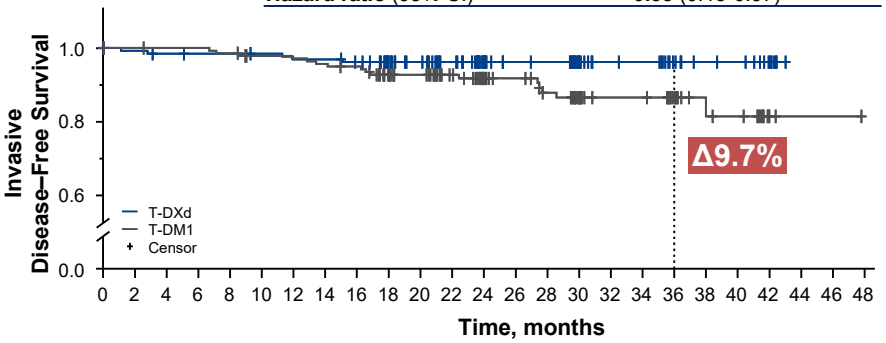


Number at risk

T-DXd	676	655	650	646	641	639	631	626	607	570	532	458	376	329	320	239	239	184	110	80	79	40	14	14	0	0	0	0
T-DM1	670	640	629	620	607	600	586	577	558	515	491	433	339	282	271	189	189	144	97	67	64	34	13	12	4	1	1	0

HER2 ISH+[b]

	T-DXd n = 140	T-DM1 n = 147
Patients with events, n (%)	**5** (3.6)	**16** (10.9)
3-year IDFS, % (95% CI)	**96.2** (91.0-98.4)	**86.5** (78.1-91.8)
Hazard ratio (95% CI)[c]	**0.35** (0.13-0.97)	



Number at risk

T-DXd	140	131	129	128	128	127	125	125	122	112	100	84	62	51	50	36	29	28	19	12	11	6	0	0	0
T-DM1	147	141	140	140	138	134	133	131	129	117	108	94	78	73	66	44	33	33	23	17	15	4	1	1	0

T-DXd demonstrated IDFS benefit over T-DM1 in both the HER2 IHC 3+ and HER2 ISH+ groups

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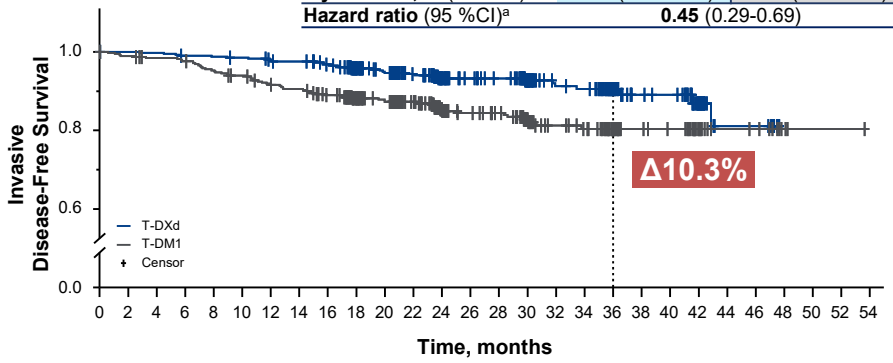
IDFS subgroup analysis: Prior neoadjuvant chemotherapy

Prior anthracyclines

	T-DXd n = 423	T-DM1 n = 399
Patients with events, n (%)	**32** (7.6)	**61** (15.3)
3-year IDFS, % (95% CI)	**90.6** (86.1-93.6)	**80.3** (74.8-84.8)
Hazard ratio (95 %CI)[a]	**0.45** (0.29-0.69)	

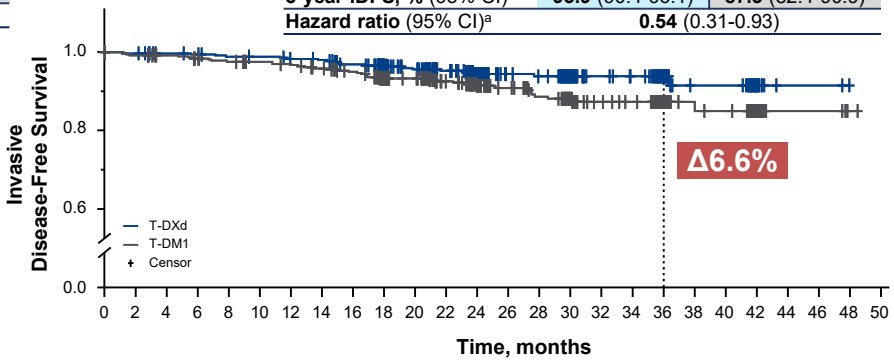


Number at risk

T-DXd	423	412	411	407	406	404	399	397	388	358	334	288	233	211	205	155	124	122	74	55	53	31	12	12	0	0	0	0
T-DM1	399	383	378	375	365	358	347	342	330	304	286	256	196	169	162	117	92	86	61	45	42	21	10	9	3	1	1	0

Prior platinum-based therapy

	T-DXd n = 386	T-DM1 n = 392
Patients with events, n (%)	**20** (5.2)	**37** (9.4)
3-year IDFS, % (95% CI)	**93.9** (90.4-96.1)	**87.3** (82.4-90.9)
Hazard ratio (95% CI)[a]	**0.54** (0.31-0.93)	



Number at risk

T-DXd	386	366	360	358	354	353	349	347	336	316	291	248	198	161	158	115	89	85	51	34	34	14	2	2	0	0
T-DM1	392	371	365	360	355	351	348	341	332	304	291	253	206	172	161	106	86	82	54	38	36	17	4	5	1	0

IDFS benefit was observed with T-DXd compared to T-DM1 regardless of prior NACT used

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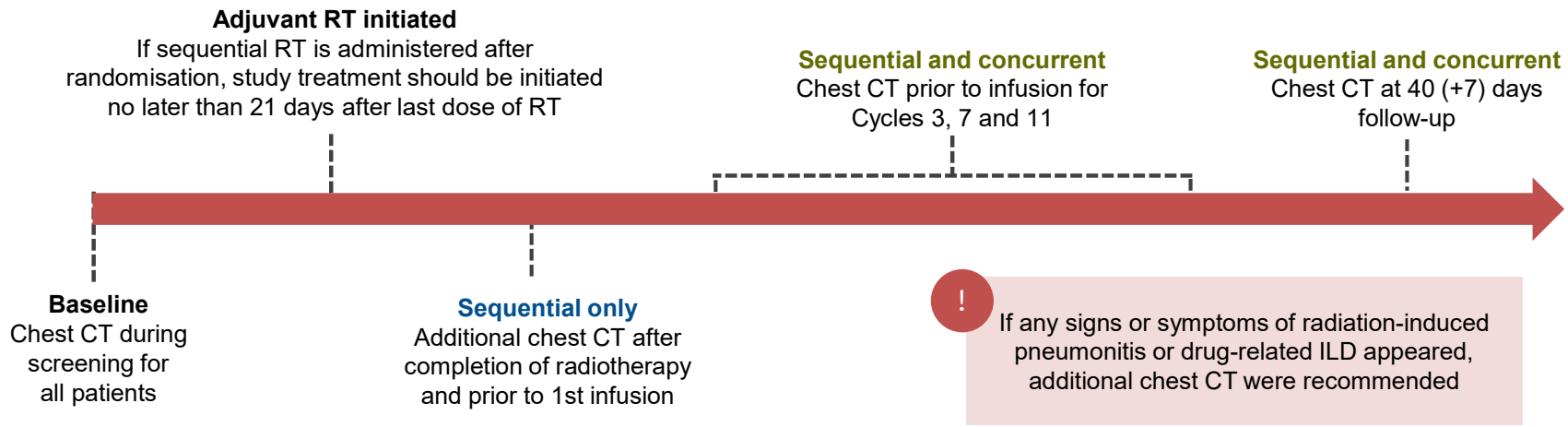
CT requirements for identifying ILD and radiation pneumonitis, as per protocol

Low-dose, non-contrast CT requirements:



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Adjudicated drug-related ILD by adjuvant RT

	T-DXd (n = 806)[a]			T-DM1 (n = 801)[a]		
Adjudicated drug-related ILD, any grade, overall, n (%)	77 (9.6)			13 (1.6)		
Adjudicated drug-related ILD, by adjuvant RT, n (%)	**SEQ (n = 319)**	**CC (n = 438)**	**SEQ or CC (n = 757)**	**SEQ (n = 270)**	**CC (n = 480)**	**SEQ or CC (n = 750)**
Any grade	34 (10.7)	42 (9.6)	76 (10.0)	7 (2.6)	5 (1.0)	12 (1.6)
Grade 1	6 (1.9)	10 (2.3)	16 (2.1)	4 (1.5)	3 (0.6)	7 (0.9)
Grade 2	24 (7.5)	27 (6.2)	51 (6.7)	3 (1.1)	2 (0.4)	5 (0.7)
Grade 3	3 (0.9)	4 (0.9)	7 (0.9)	0	0	0
Grade 4	0	0	0	0	0	0
Grade 5[b]	1 (0.3)	1 (0.2)	2 (0.3)	0	0	0
Time to onset, median (range), days[c]	122.0 (36-350)	124.5 (37-326)	123.5 (36-350)	79.0 (36-142)	121.0 (78-130)	121.0 (36-142)
Duration, median (95% CI), days[d,e]	77.0 (41-114)	67.0 (43-107)	74.0 (46-106)	114.0 (22-NE)	142.0 (51-NE)	114.0 (51-235)

- Timing of adjuvant RT did not impact incidence or severity of adjudicated drug-related ILD in either arm
- In the T-DXd arm, adjuvant RT timing had no effect on time to onset or duration of adjudicated drug-related ILD
- Most patients with drug-related ILD had recovered or were recovering at the data cutoff

CC, concurrent; ILD, interstitial lung disease; RT, radiotherapy; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least one dose of study treatment. [b]Grade 5 adjudicated drug-related ILD was reported in 2 patients (0.2%) in the T-DXd arm, one at cycle 6 and one at cycle 7. In these 2 patients, treatment management guidelines were not appropriately followed, emphasizing the importance of appropriate identification of and adherence to guidelines. [c]Time to first adjudicated ILD onset = onset date of first ILD adjudicated as drug-related - first dose date + 1. [d]Median is based on Kaplan-Meier Estimate. CIs were computed using the Brookmeyer-Crowley method.
[e]Duration of first ILD = investigator reported end date - investigator reported onset date + 1. End date will be censored for ongoing ILDs.

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Investigator-reported radiation pneumonitis by adjuvant RT

	T-DXd[a]			T-DM1[a]		
	SEQ (n = 319)	CC (n = 438)	SEQ or CC (n = 757)	SEQ (n = 270)	CC (n = 480)	SEQ or CC (n = 750)
Investigator-reported RP,[b] any grade, n(%)	110 (34.5)	128 (29.2)	238 (31.4)	101 (37.4)	128 (26.7)	229 (30.5)
Grade 1	97 (30.4)	104 (23.7)	201 (26.6)	82 (30.4)	95 (19.8)	177 (23.6)
Grade 2	13 (4.1)	24 (5.5)	37 (4.9)	19 (7.0)	33 (6.9)	52 (6.9)
Grade ≥3	0	0	0	0	0	0
Time to onset, median (range), days[c]	146.5 (46-334)	123.0 (39-353)	124.0 (39-353)	110.0 (56-260)	122.5 (28-232)	120.0 (28-260)
Duration, median (95% CI), months[d,e]	13.5 (11.0-19.9)	9.6 (6.6-12.2)	11.6 (9.6-13.5)	10.1 (9.5-14.7)	9.8 (7.7-12.9)	10.1 (9.2-12.4)

- In both arms, all RP events were grade ≤2, although patients treated with sequential adjuvant RT reported higher incidences of investigator-reported RP than those treated with concurrent adjuvant RT
- Most patients with RP events had recovered or were recovering at data cutoff; rates of unrecovered/unresolved RP were higher among patients who received sequential RT prior to T-DXd compared with T-DM1 (54.5% vs 39.6%)
- In the T-DXd arm, patients receiving sequential adjuvant RT showed longer time to onset and duration of RP than those who received concurrent adjuvant RT

CC, concurrent; RP, radiation pneumonitis; RT, radiotherapy; SEQ, sequential; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least 1 dose of study treatment. [b]Grouped term. Includes the preferred terms pulmonary radiation injury, radiation alveolitis, radiation bronchitis, radiation fibrosis – lung, radiation pneumonitis. [c]Time to first investigator-reported RP onset = onset date of first investigator-reported RP – start date of radiotherapy + 1. [d]Duration of first Investigator Reported RP = investigator reported end date - investigator reported onset date + 1. End date will be censored for ongoing events. [e]Median is based on Kaplan-Meier Estimate. CIs were computed using the Brookmeyer-Crowley method.

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DESTINY-Breast05 Conclusions/SABCS Updates

- IDFS improvement with T-DXd compared with T-DM1 was consistent across subgroups, regardless of:
  - Prior NACT (anthracyclines or platinum-based therapy)
  - HER2 status (IHC 3+ or HER2 IHC 2+/1+ and ISH+)
- Timing of adjuvant RT did not impact incidence or severity of drug-related ILD
  - Most patients who experienced ILD had recovered or were recovering
- Overall, T-DXd demonstrated a manageable safety profile with both sequential and concurrent adjuvant RT
- Statistical decrease in CNS recurrences although numbers were small- 2.1% with TDX-D vs 3.1 % with TDM-1
- T-DXd represents a new potential standard of care in the post neoadjuvant HER-2 positive residual disease setting

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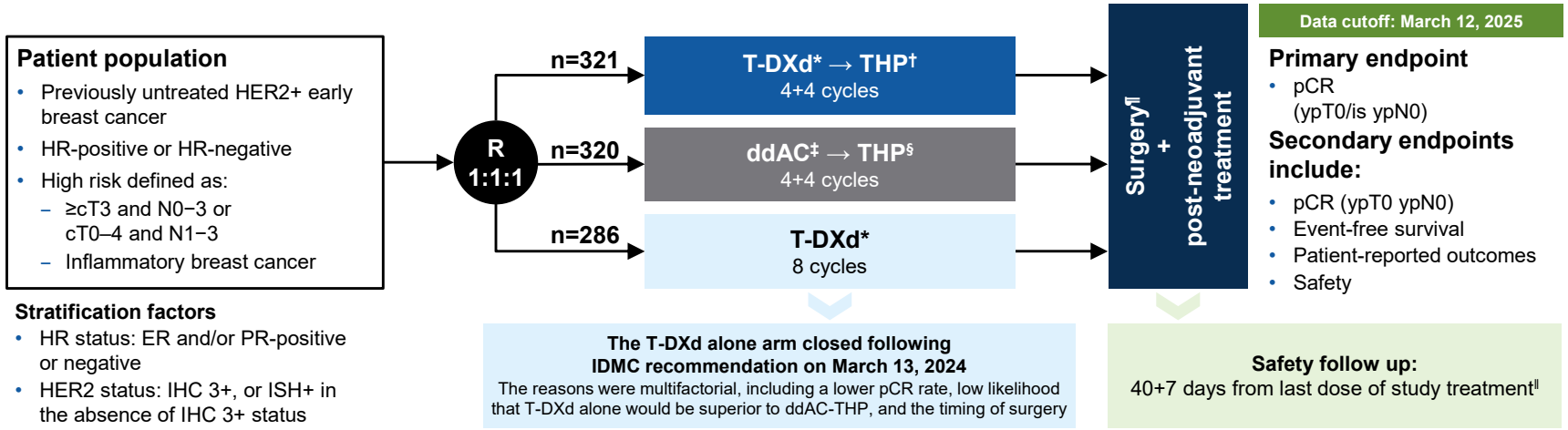
DESTINY-Breast11 study design

A randomized, global, multicenter, open-label, Phase 3 study (NCT05113251)[1,2]



- Chest HRCT scans were performed at screening, Q6W until EOT, at safety follow up, and if ILD/pneumonitis was suspected
  - If ILD/pneumonitis was confirmed, follow up continued until resolution; potential cases were retrospectively evaluated by an independent ILD Adjudication Committee
- Heart failure adverse events were recorded until EOT and at end of study (up to 6 years' follow up)

Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at EOT to assess left ventricular ejection fraction

*5.4 mg/kg Q3W; †paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); §paclitaxel (80 mg/m^2 QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖for patients who completed study treatment, this should take place after surgery; if all study treatments discontinued prior to completion of planned cycles, this could be prior to surgery. cT, clinical tumor stage; ddAC, dose-dense doxorubicin + cyclophosphamide; EOT, end of treatment; ER, estrogen receptor; HER2, human epidermal growth factor receptor; HER2+, HER2-positive; HR, hormone receptor; HRCT, high-resolution computed tomography; IDMC, Independent Data Monitoring Committee; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; pCR, pathologic complete response; PR, progesterone receptor; QXW, every X weeks; R, randomized; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab; ypT0 ypN0, absence of invasive and in situ cancer in the breast and axillary nodes; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes

1. Harbeck N, et al. Oral presentation at ESMO 2025 (Abstract 4100); 2. NCT05113251. Updated November 18, 2025. Available from: https://www.clinicaltrials.gov/study/NCT05113251 (Accessed December 1, 2025)

Patient demographics and key baseline characteristics

		T-DXd-THP (n=321)	ddAC-THP (n=320)	T-DXd (n=286)
Median (range) age, years		50 (25–82)	50 (23–79)	50 (23–79)
Female, n (%)		321 (100)	320 (100)	286 (100)
Geographical region, n (%)	Asia	152 (47.4)	152 (47.5)	124 (43.4)
	Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
	North America	43 (13.4)	41 (12.8)	52 (18.2)
	Rest of world*	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)†	Asian	160 (49.8)	157 (49.1)	127 (44.4)
	White	140 (43.6)	137 (42.8)	139 (48.6)
	Black or African American	5 (1.6)	7 (2.2)	7 (2.4)
	Other	12 (3.7)	10 (3.1)	8 (2.8)
Eastern Cooperative Oncology Group performance status score, n (%)	0	278 (86.6)	280 (87.5)	252 (88.1)
	1	43 (13.4)	40 (12.5)	34 (11.9)
HER2 status, n (%)‡	IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
	Other	40 (12.5)	36 (11.3)	32 (11.2)
HR status, n (%)§	Positive¶	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage, n (%)	cT0–2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3–4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status, n (%)‖	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

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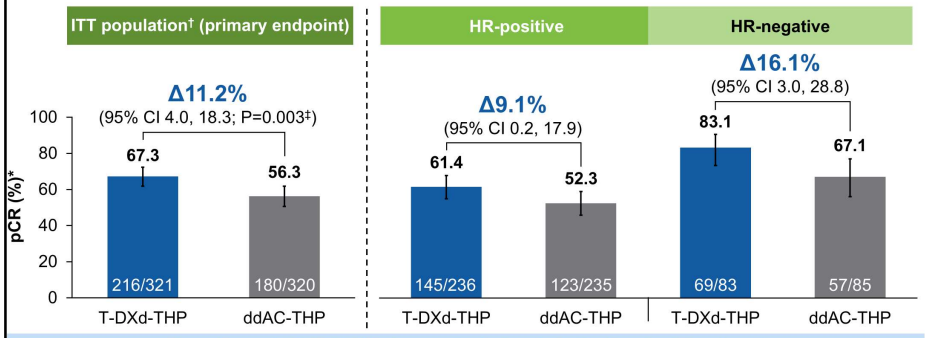
pCR (ypT0/is ypN0): primary endpoint



Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP
Improvement was observed in both the HR-positive and HR-negative subgroups

pCR higher in HR- v HR+

pCR higher for TDX-d in all groups

pCR (ypT0/is ypN0) by subgroups

		pCR rate, % (n/N) T-DXd-THP (n=321)	pCR rate, % (n/N) ddAC-THP (n=320)	ΔpCR, % (95% CI)
All patients		67.3 (216/321)	56.3 (180/320)	11.2 (4.0, 18.3)
Age at baseline	<65 years	66.7 (188/282)	58.0 (167/288)	8.7 (0.7, 16.5)
	≥65 years	71.8 (28/39)	40.6 (13/32)	31.2 (8.0, 51.4)
Geographical region	Asia	66.5 (101/152)	56.6 (86/152)	9.9 (−1.1, 20.6)
	Western Europe	75.4 (52/69)	62.3 (48/77)	13.0 (−2.2, 27.5)
	North America	74.4 (32/43)	36.6 (15/41)	37.8 (16.8, 55.7)
	Rest of world*	54.4 (31/57)	62.0 (31/50)	−7.6 (−25.7, 11.2)
Eastern Cooperative Oncology Group performance status score	0	68.7 (191/278)	55.7 (156/280)	13.0 (5.0, 20.9)
	1	58.1 (25/43)	60.0 (24/40)	−1.9 (−22.6, 19.1)
Menopausal status	Post	68.8 (86/125)	56.9 (87/153)	11.9 (0.5, 23.0)
	Pre	66.9 (123/184)	55.2 (90/163)	11.6 (1.4, 21.7)
HER2 status	IHC 3+	71.1 (199/280)	61.5 (174/283)	9.6 (1.8, 17.3)
	Other	42.5 (17/40)	16.7 (6/36)	25.8 (5.2, 44.4)
HR status	Positive	61.4 (145/236)	52.3 (123/235)	9.1 (0.2, 17.9)
	Negative	83.1 (69/83)	67.1 (57/85)	16.1 (3.0, 28.8)
American Joint Committee on Cancer clinical stage	II–IIIA	65.7 (163/248)	56.4 (146/259)	9.4 (0.9, 17.7)
	IIIB–IIIC	72.2 (52/72)	55.7 (34/61)	16.5 (0.1, 32.3)
Nodal status	N0	57.7 (15/26)	57.1 (20/35)	0.6 (−24.2, 24.8)
	N+	68.3 (196/287)	56.6 (159/281)	11.7 (3.8, 19.5)

Improvement in pCR for T-DXd-THP vs ddAC-THP was observed across most pre-specified subgroups

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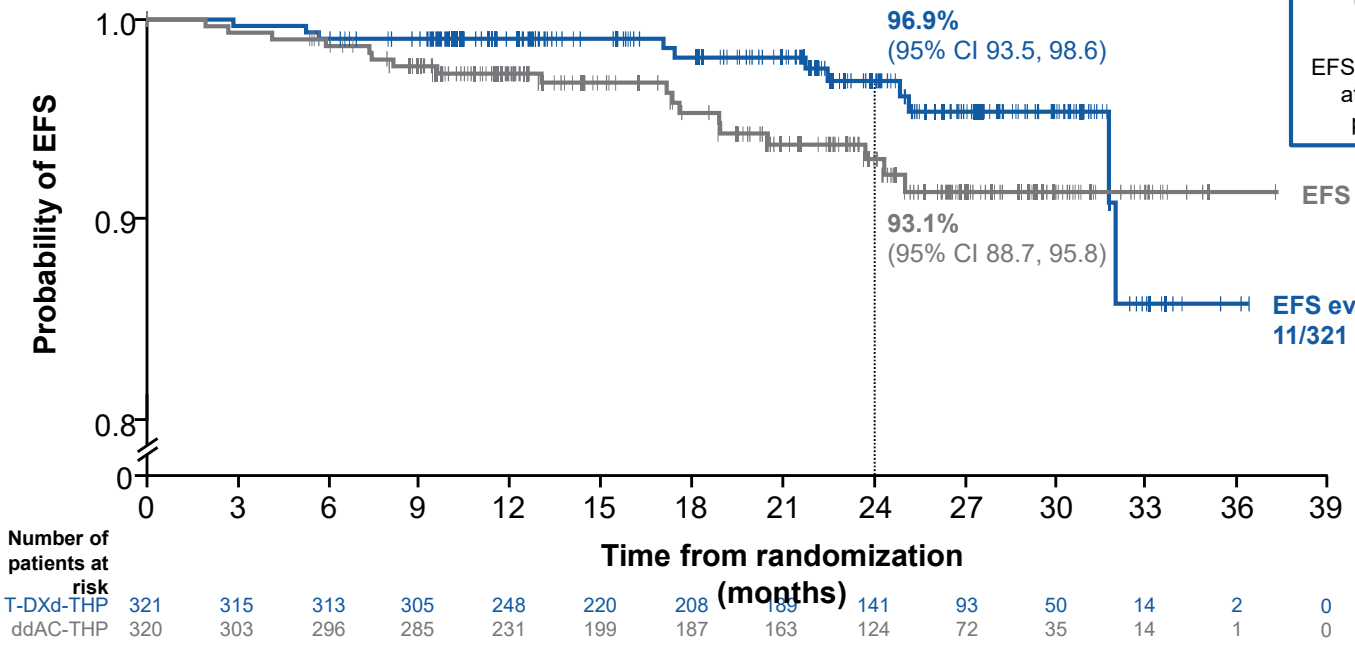
EFS



An early positive trend in EFS was observed, favoring T-DXd-THP vs ddAC-THP

The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

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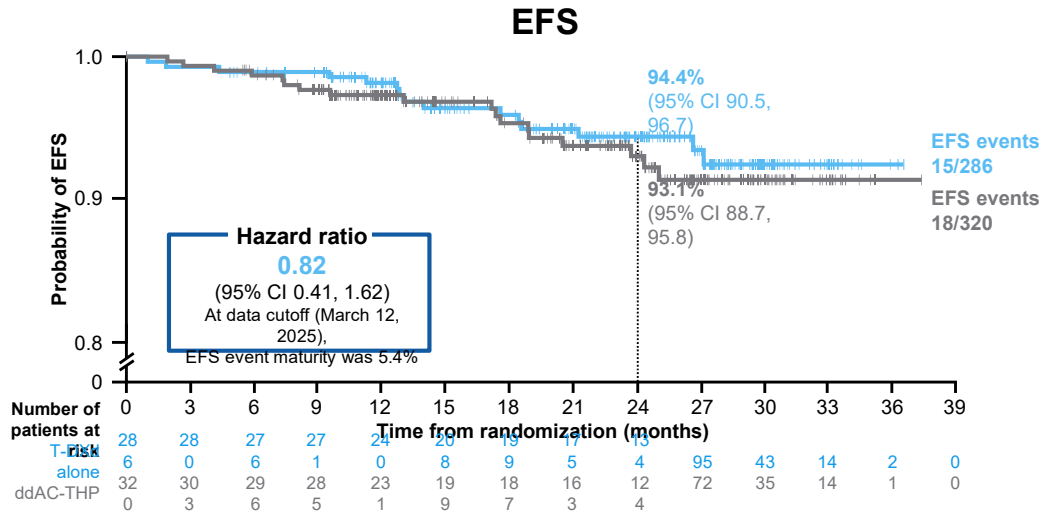
T-DXd alone arm: efficacy summary

On March 13, 2024, the T-DXd alone arm closed following Independent Data Monitoring Committee recommendation.*
Patients who were still receiving T-DXd alone could remain on therapy or immediately switch to local SOC

pCR rate

%	T-DXd (n=286)	ddAC-THP (n=320)
Primary analysis Switch to local SOC classified as non-pCR		
pCR†	43.0	56.3
Δ (95% CI)	−13.2 (−20.8, −5.4)	
Prespecified supplementary analysis Switch to local SOC not automatically classified as non-pCR		
pCR†	51.4	57.2
Δ (95% CI)	−5.8 (−13.4, 1.9)	



T-DXd alone showed inferior but robust pCR compared with the five-agent ddAC-THP
EFS data were similar for T-DXd alone and ddAC-THP

Treatment effects were estimated by the difference in pCR with 95% CIs based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights). Median duration of follow up was 24.9 months (T-DXd) and 23.6 months (ddAC-THP). Analyses are reported in the ITT population. *The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery; †by blinded central review

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DESTINY-Breast11 safety: neoadjuvant trastuzumab deruxtecan (T-DXd) alone or followed by paclitaxel + trastuzumab + pertuzumab (THP) vs dose-dense doxorubicin + cyclophosphamide followed by THP (ddAC-THP) in high-risk, HER2+ early-stage breast cancer

RF6-02
Wednesday, December 10, 2025

Giuseppe Curigliano, MD, PhD
Division of Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milano, Italy
Department of Oncology and Hematology-Oncology, University of Milano, Milano, Italy

Co-authors: Nadia Harbeck, Jean-François Boileau, Shanu Modi, Jiong Wu, Shinji Ohno, Catherine Kelly, Xuchen Cao, Alessandra Fabi, Santiago Escrivá-de-Romaní, Akihiko Shimomura, Éric Poirier, Rona Joseph, Lasika Seneviratne, Shin-Cheh Chen, Maria Luisa Tiambeng, José Luiz Pedrini, Maria Schwaederle, Mohammad Gufran, Annie Darilay, Lajos Pusztai
On behalf of the DESTINY-Breast11 investigators

DESTINY Breast11

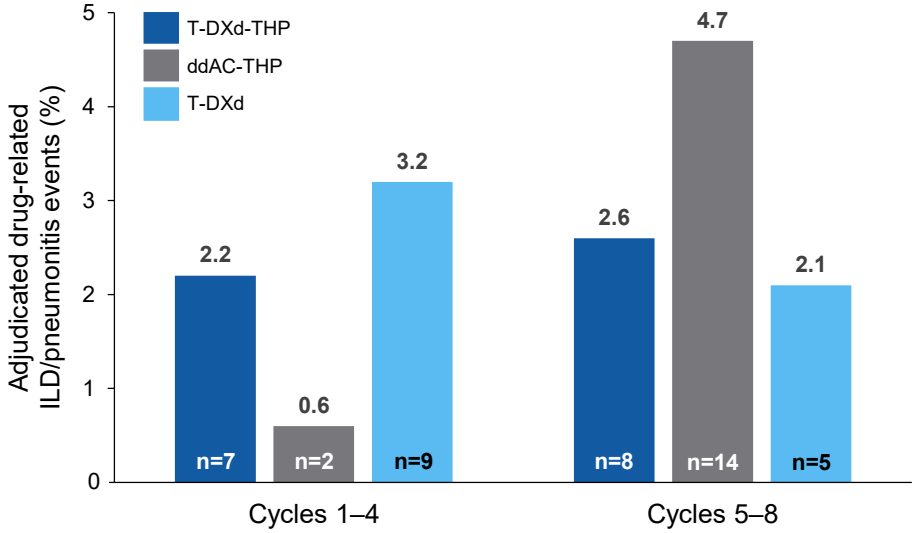
Adjudicated drug-related ILD/pneumonitis: events by cycle

n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All grade	14 (4.4)	16 (5.1)	14 (4.9)
Grade 1	4 (1.3)	4 (1.3)	2 (0.7)
Grade 2	8 (2.5)	6 (1.9)	12 (4.2)
Grade 3	1 (0.3)	5 (1.6)	0
Grade 4	0	0	0
Grade 5	1 (0.3)	1 (0.3)	0
Grade ≥3	2 (0.6)	6 (1.9)	0

Median (range) time to onset:

- **82.5 (32–184) days** (T-DXd-THP; n=14)*
- **77.0 (41–149) days** (ddAC-THP; n=16)†
- **78.0 (25–155) days** (T-DXd; n=14)

Adjudicated drug-related ILD/pneumonitis by cycle of onset‡



All-grade adjudicated drug-related ILD/pneumonitis rates were low and similar across all arms, and Grade ≥3 events were most frequent with ddAC-THP

Rates remained stable (T-DXd-THP) and were higher (ddAC-THP) in the THP phase (Cycles 5–8) vs Cycles 1–4

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Adjudicated drug-related ILD/pneumonitis: treatment discontinuations, interruptions, reductions, and SAEs

Adjudicated drug-related ILD/pneumonitis, n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
Leading to treatment discontinuation	6 (1.9)	7 (2.2)	9 (3.2)
Grade 1	0	0	2 (0.7)
Grade 2	5 (1.6)	4 (1.3)	7 (2.5)
Grade 3	0	3 (1.0)	0
Grade 5	1 (0.3)	0*	0
Leading to treatment interruption	3 (0.9)	6 (1.9)	3 (1.1)
Grade 1	1 (0.3)	2 (0.6)	0
Grade 2	1 (0.3)	0	3 (1.1)
Grade 3	1 (0.3)	4 (1.3)	0
Leading to dose reduction	0	0	0
SAE	2 (0.6)	9 (2.9)	1 (0.4)

The incidence of treatment discontinuations and interruptions due to ILD/pneumonitis were low across treatments, with no dose reductions, and there were more SAEs in the ddAC-THP arm compared with T-DXd-THP and T-DXd arms

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Left ventricular dysfunction

n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
Left ventricular dysfunction	4 (1.3)	19 (6.1)	2 (0.7)
Grade 1	0	3 (1.0)	0
Grade 2	3 (0.9)	10 (3.2)	2 (0.7)
Grade 3	1 (0.3)	6 (1.9)	0
Grade ≥3	1 (0.3)	6 (1.9)	0
Ejection fraction decreased	4 (1.3)	15 (4.8)	2 (0.7)
Grade 2	3 (0.9)	9 (2.9)	2 (0.7)
Grade 3	1 (0.3)	6 (1.9)	0
Grade ≥3	1 (0.3)	6 (1.9)	0
Cardiac failure	0	4 (1.3)	0
Grade 1	0	3 (1.0)	0
Grade 2	0	1 (0.3)	0

Rates of all-grade and Grade ≥3 left ventricular dysfunction were higher with ddAC-THP vs T-DXd-THP and T-DXd, and there were no events of cardiac failure in the T-DXd-containing arms

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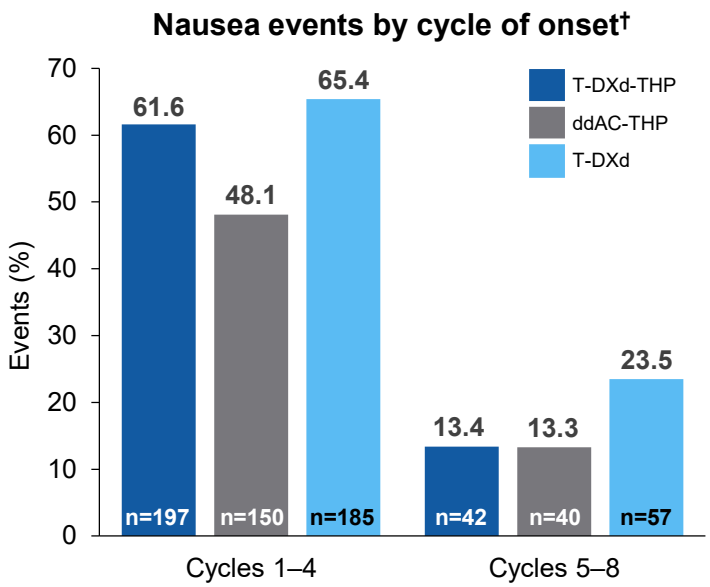
Nausea and vomiting: events by cycle and antiemetic use

n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All-grade nausea	207 (64.7)	161 (51.6)	193 (68.2)
Grade ≥3	6 (1.9)	1 (0.3)	3 (1.1)
All-grade vomiting	92 (28.8)	66 (21.2)	88 (31.1)
Grade ≥3	3 (0.9)	2 (0.6)	3 (1.1)

Per the protocol, prophylaxis with 2–3 antiemetics* prior to each dose of T-DXd was recommended, but not mandated

Protocol-recommended antiemetics on or prior to Cycle 1 Day 1*			
3-antiemetic regimen	54 (16.9)	124 (39.7)	40 (14.1)
2-antiemetic regimen	183 (57.2)	126 (40.4)	157 (55.5)
All antiemetics on or prior to Cycle 1 Day 1	284 (88.5)	282 (88.1)	240 (83.9)
≥3-antiemetic regimen	105 (32.8)	174 (55.8)	77 (27.2)



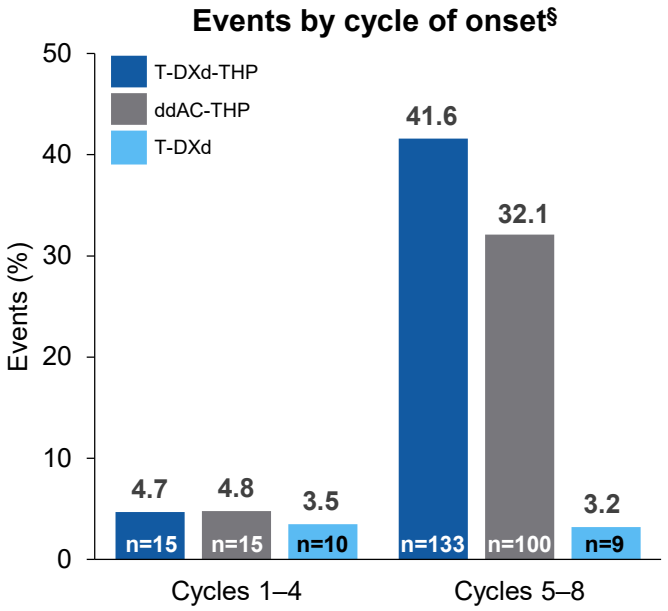
Vomiting events occurred with a similar trend by cycle of onset

Nausea and vomiting events were generally low grade, and rates decreased substantially after Cycles 1–4; use of ≥3 antiemetics was much greater with ddAC-THP than with T-DXd-THP and T-DXd

Safety analyses included all patients who received at least one dose of any study treatment
*Use of 2 or 3 of the following was recommended by the protocol: a glucocorticoid, serotonin (5-HT3) receptor antagonist, and a neurokinin-1 receptor antagonist; †percentages are calculated using the number of patients at risk at any point in the cycle window as the denominator; if a patient has occurrences in different cycles, the patient may be counted in multiple cycles

Peripheral neuropathy*

Peripheral neuropathy, n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All grade, n (%)	144 (45.0)	112 (35.9)	19 (6.7)
Grade 1	80 (25.0)	75 (24.0)	18 (6.4)
Grade 2	58 (18.1)	31 (9.9)	1 (0.4)
Grade 3	6 (1.9)	6 (1.9)	0
Grade ≥3	6 (1.9)	6 (1.9)	0
Possibly treatment related	137 (42.8)	105 (33.7)	16 (5.7)
SAE	0	0	0
Leading to treatment discontinuation†	7 (4.9)	7 (6.3)	0
Leading to treatment interruption†	3 (2.1)	3 (2.7)	0
Leading to dose reduction†	25 (17.4)	12 (10.7)	0
Median (range) days to first onset‡	113.0 (1–189)	89.5 (8–167)	72.0 (1–162)



Although rates of peripheral neuropathy were higher with T-DXd-THP than T-DXd and ddAC-THP, events were non-serious and generally low grade, and most occurred during the THP phase (Cycles 5–8)

Safety analyses included all patients who received at least one dose of any study treatment
*Grouped term defined using the narrow Standardised MedDRA Query 'peripheral neuropathy'; †the denominator is the number of patients with peripheral neuropathy; ‡calculated as: date of onset of the patient's first event − date of the first dose + 1; §percentages are calculated using the number of patients at risk at any point in the cycle window as the denominator; if a patient has occurrences in different cycles, the patient may be counted in multiple cycles

DESTINY Breast11 Conclusions

- T-DXd-THP showed a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP: Δ11.2% in a high-risk population with high percentage of HR positive patients
- An early positive trend in EFS was observed, favoring T-DXd-THP
- AEs were manageable
  - Rates of drug-related ILD/pneumonitis were low across arms
  - Rates of LV dysfunction were lower with T-DXd-THP than ddAC-THP
  - Rates of nausea and vomiting were higher with T-DXd-THP than ddAC-THP
  - Rates of hematologic toxicities were lower with T-DXd-THP than ddAC-THP
  - Rates of peripheral neuropathy were higher with T-DXd-THP than T-DXd and ddAC-THP
- This data supports TDXd-THP as a potential new neoadjuvant treatment option for high-risk HER-2 + early breast cancer

Biomarker Analysis

- Many patients with HER-2 positive disease are ultimately cured
- Newer therapies are improving pCR rates and those without pCR benefit from escalating therapy in the adjuvant setting
- pCR is prognostic but not completely sensitive or specific
- Better biomarkers are needed to help guide treatment and assess prognosis

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
DECEMBER 9–12, 2025
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

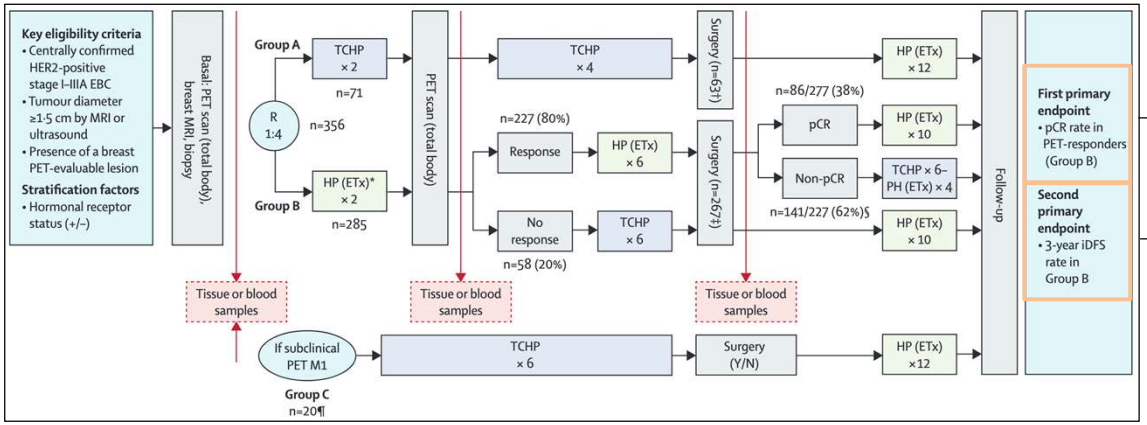
Circulating tumor DNA (ctDNA) in HER2+ Early Breast Cancer: A translational analysis of PHERGain

Antonio Llombart-Cussac[1,2,3], José Manuel Pérez-García[1,4], Manuel Ruiz-Borrego[5], Agostina Stradella[6], Begoña Bermejo[7,8], Santiago Escrivá-de-Romaní[9], Cristina Reboredo[10], Nuria Ribelles[11], Alfonso Cortés-Salgado[12], Cinta Albacar[13], Marco Colleoni[14], Gabriele Antonarelli[15,16], Giulia Notini[1], Maria Gion[11,17], Juan José García-Mosquera[1,18], Lucia Sanz[17], Miquel Quintana[1], Elena Martinez-Garcia[1], Paula González-Alonso[1], Ana Amaya-Garrido[1], José Antonio Guerrero[1], Jose Rodríguez-Morató[1], Leonardo Mina[1], Griselda Martrat[1], François Riva[19], Derek Dustin[19], Haiyang Zhang[19], Mario Mancino[1], Javier Cortés[1,4,17,20,21]

[1]Medica Scientia Innovation Research (MedSIR), Barcelona, Spain and Ridgewood, New Jersey, US; [2]Hospital Arnau de Vilanova, FISABIO, Valencia, Spain; [3]Translational Oncology Group, Department of Medicine, Facultad de Ciencias de la Salud, Universidad Cardenal Herrera-CEU, Alfara del Patriarca, Spain; [4]International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; [5]Virgen del Rocío University Hospital, Sevilla, Spain; [6]Medical Oncology Department, Institut Català D'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; [7]Medical Oncology, Hospital Clínico Universitario de Valencia, Biomedical Research Institute INCLIVA, Valencia; Medicine Department, Universidad de Valencia; [8]Oncology Biomedical Research National Network (CIBERONC-ISCIII), Madrid; [9]Medical Oncology Department, Breast Cancer Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Hospital Universitario A Coruña, Breast Cancer Unit, A Coruña, Spain; [11]UGC Oncología Intercentros. Hospitales Universitarios Regional y Virgen de la Victoria de Málaga. Instituto de Investigaciones Biomédicas de Málaga (IBIMA), Málaga, Spain; [12]Universidad de Alcalá. Medical Oncology Department, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain; [13]Institut d'Oncologia de la Catalunya Sud (IOCS), Hospital Universitari Sant Joan de Reus, IISPV, Reus, Spain; [14]Instituto Europeo di Oncologia (IEO), IRCCS, Milan, Italy; [15]Department of Oncology and Hemato-Oncology (DIPO), University of Milan, Milan, Italy; [16]Division of Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan, Italy; [17]IOB Madrid, Hospital Beata María Ana, Madrid, Spain ; [18]Dr. Rosell Oncology Institute (IOR), Dexeus University Hospital, Pangaea Oncology, Quironsalud Group, 08028, Barcelona, Spain; [19]Guardant Health, Palo Alto, CA, USA; [20]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [21]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid, Spain.

Introduction

- **HER2-directed therapies** have improved the outcome of patients with HER2[+] early breast cancer (EBC), leading to de-escalation approaches[1].
- The **PHERGain study:** PET-guided, pathological complete response (pCR)-adapted strategy to omit chemotherapy (CT) in patients with HER2[+] EBC undergoing neoadjuvant dual HER2 blockade with trastuzumab and pertuzumab (HP)[2,3].

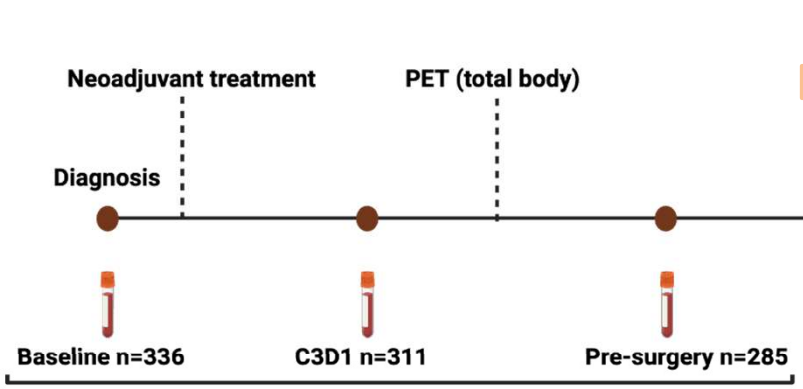


Omission of CT in **37.9% of patients**[1].

3-year invasive-disease free survival **(iDFS) rate of 94.8%**[2].

1. Lin NU et al., *J Clin Oncol*. 2015
2. Perez-García JM *et al., Lancet Oncol.* 2021
3. Perez-García JM et al., *Lancet.* 2024

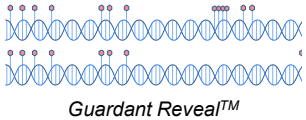
PHERGuide: methodology and objectives



Objective 1: assess the correlation between ctDNA detection and pCR

Objective 2: evaluate the association between ctDNA detection and/or clearance with patient outcomes

ctDNA isolation and analysis



Guardant Reveal™

Tissue-free epigenomic assay:

ctDNA detection+estimated tumor fraction

Llombart-Cussac A, et al. Presented at 2025 San Antonio Breast Cancer Symposium. December 9-12, 2025. San Antonio, Texas. Reprinted with Permission.

PHERGuide Conclusions

- ctDNA was detected in 71% of baseline samples.
  - Positive ctDNA was associated with higher clinical stage and nodal involvement.
  - There was no correlation between baseline ctDNA presence and pCR rates
  - Absence of ctDNA at baseline was associated with excellent outcomes-3 year DFS of 100%
- ctDNA clearance at cycle 3 and pre-surgery was associated with higher pCR rate and lower iDFS event risk
- ctDNA positivity at C3D1 was not significantly associated with a worse 3-year iDFS. However, the design of the study included treatment changes (chemotherapy) for non PET-responder
- No patient with detectable ctDNA prior to surgery (n=28) achieved a pCR.
- ctDNA positivity prior to surgery was associated with a worse 3-year iDFS rate

Early-Stage HER-2 + Breast Cancer Conclusions

- T-Dxd in the HER-2 + residual disease setting improves outcomes in all comers including high risk patients regardless of NA regimen and HER-2 status (IHC 2+ vs 3+) representing a potential new standard of care
- Incorporating T-Dxd into neoadjvant regimens for high-risk HER-2+ early disease improves pathologic response rates with trends towards improved event free survival. This represents a potential new standard of care
- ctDNA analysis demonstrates prognostic significance but studies do not yet demonstrate interventions altering clinical outcomes. These markers do not yet represent a standard of care

Early-Stage HER-2+ Breast Cancer-Questions/Challenges/Answers Post SABCS

- Can we improve outcomes for patients with residual disease after NA therapy? Yes, but…
  - Does everyone need T-DXd or just high-risk patients?
- Should we use T-DXd in the NA setting? Probably yes, but…
  - How do we select appropriate patients?
  - Is the DB11 data applicable if we are using TCHP as our standard of care rather than AC-THP?
  - If patients receive T-DXd in the NA setting, what do we do for patients with residual disease at surgery?
  - If we move our most effective drugs up front, what do we do when patients progress?
- Can we use biomarkers to help predict pathologic response and outcomes (yes) and help tailor our treatment recommendations (hopefully)?
  - We need to fine tune our biomarker analysis to help identify patients who may be candidates for less aggressive therapy and those who benefit from more intensive therapy

HR positive/HER2 negative Early-Stage Breast Cancer

Melissa McShane, MD

Fox Chase Cancer Center

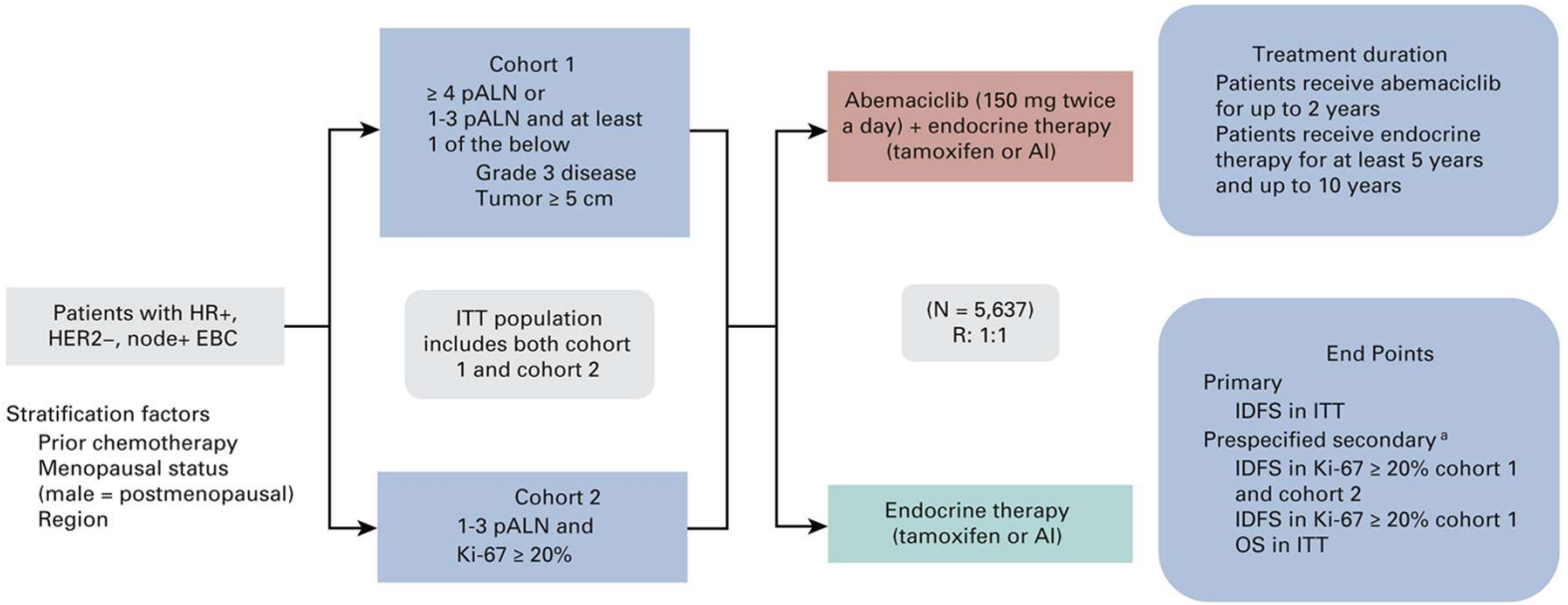
Outline

- Adjuvant CDK 4/6 inhibitors
  - monarchE
  - NATALEE
- lidERA Trial — SERD Giredestrant
- Artificial Intelligence (AI) in the Adjuvant Setting

Selecting Adjuvant CDK 4/6 Inhibitors

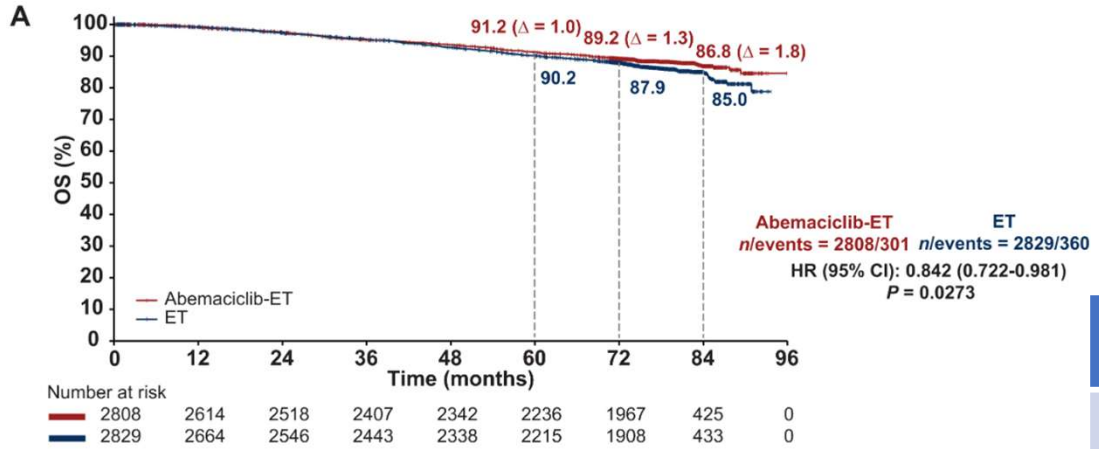
- Both abemaciclib and ribociclib are approved for adjuvant use
- Several differences between the 2 studies (duration, dose intensity, patient population, etc.)
- Updated results from both monarchE (abemaciclib) and NATALEE (ribociclib) presented at ESMO 2025

monarchE- Study Design

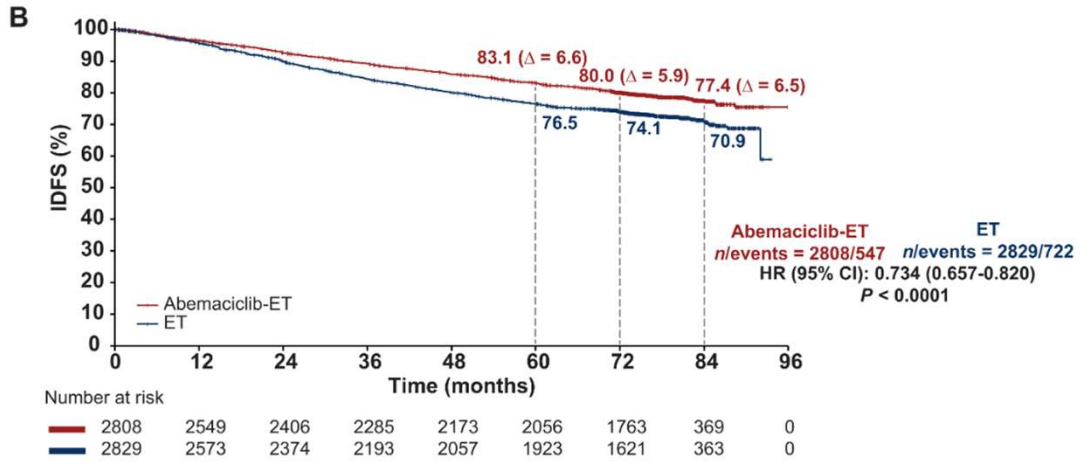


ASCO Daily News, February 2022

Overall Survival



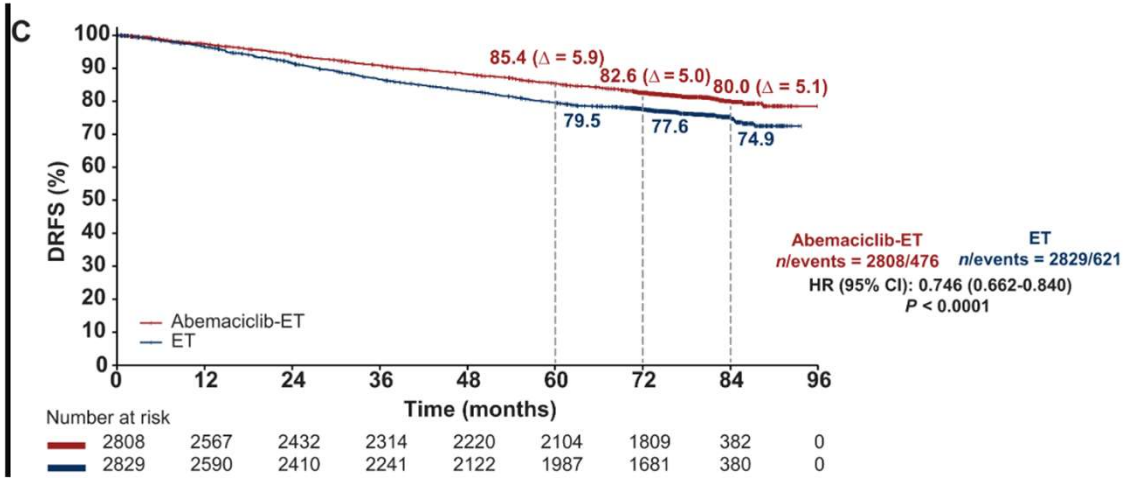
Invasive DFS



Updated Results- ESMO 2025

	Abemaciclib + ET	ET	HR
Overall Survival	86.8%	85%	0.842
Invasive DFS	77.4%	70.9%	0.734
DRFS	80.0%	74.9%	0.746

ESMO 2025
Johnston et al, Annals of Oncology, 2025



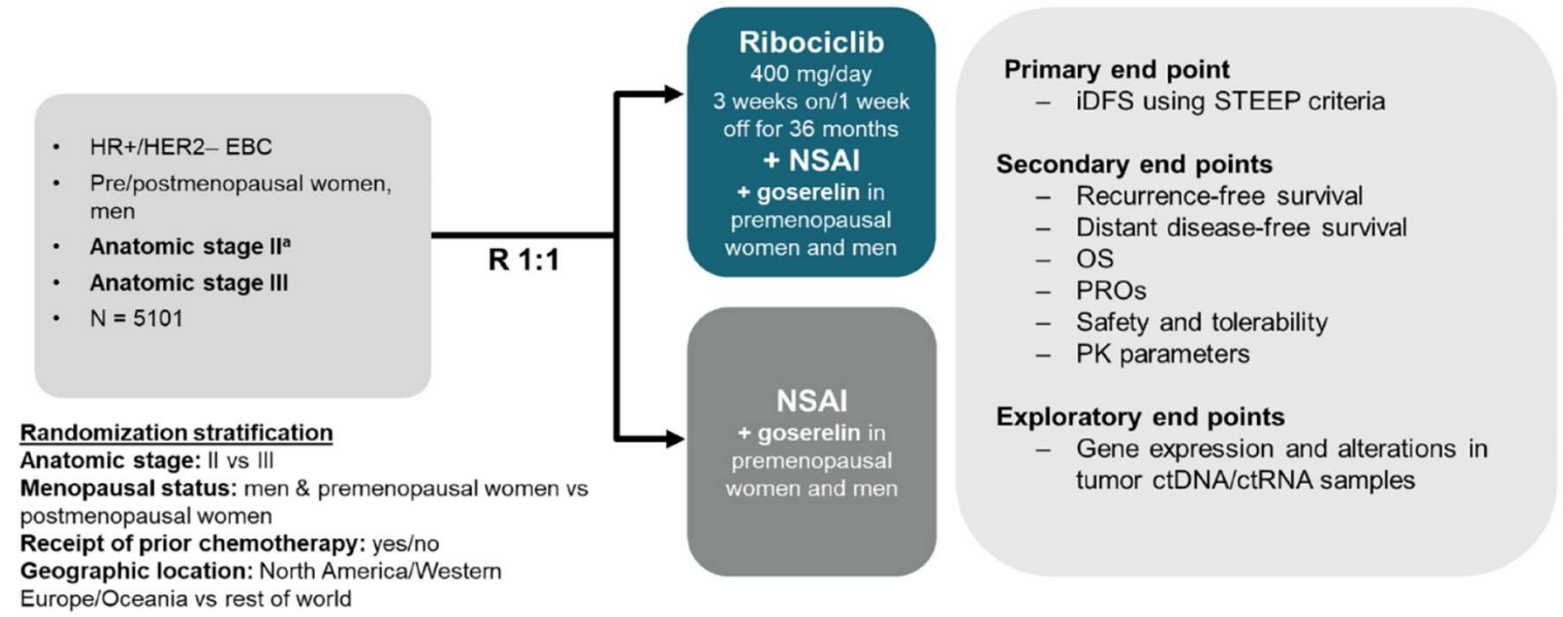
Distant Relapse Free Survival

Updated Results- ESMO 2025

	Abemaciclib + ET	ET	HR
Overall Survival	86.8%	85%	0.842
Invasive DFS	77.4%	70.9%	0.734
DRFS	80.0%	74.9%	0.746

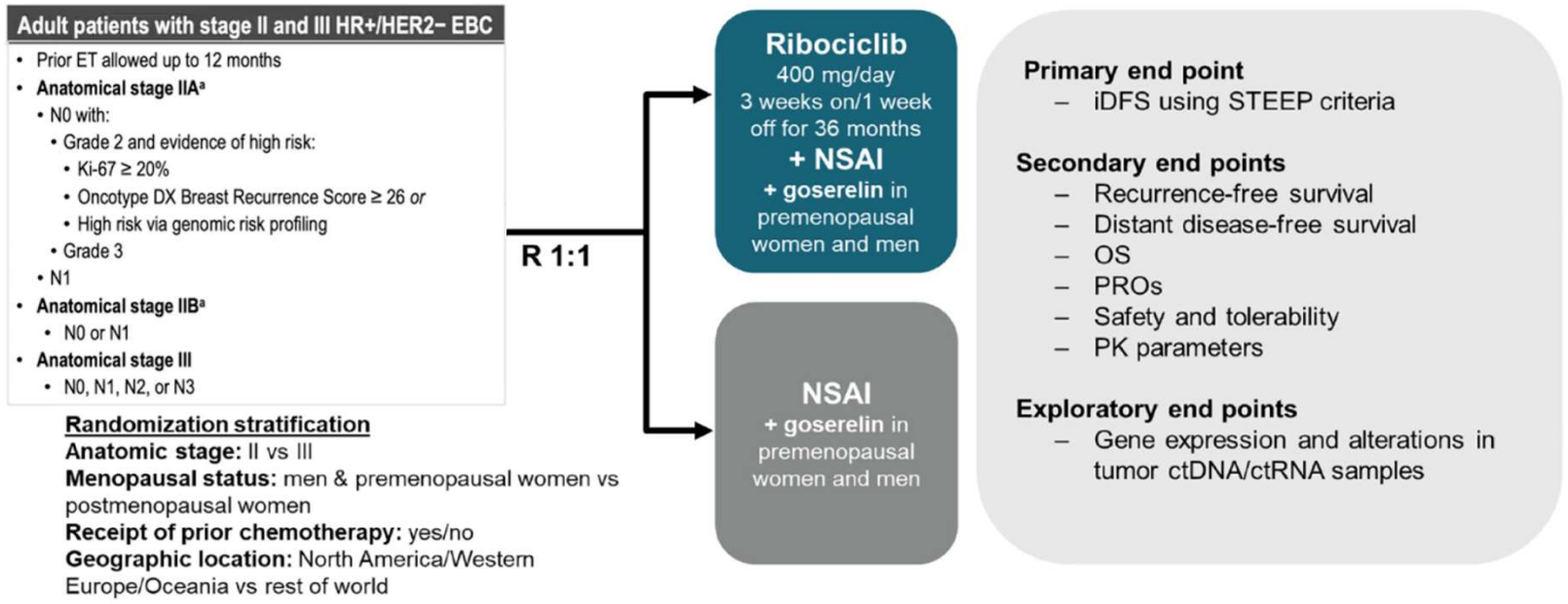
ESMO 2025
Johnston et al, Annals of Oncology, 2025

NATALEE- Study Design



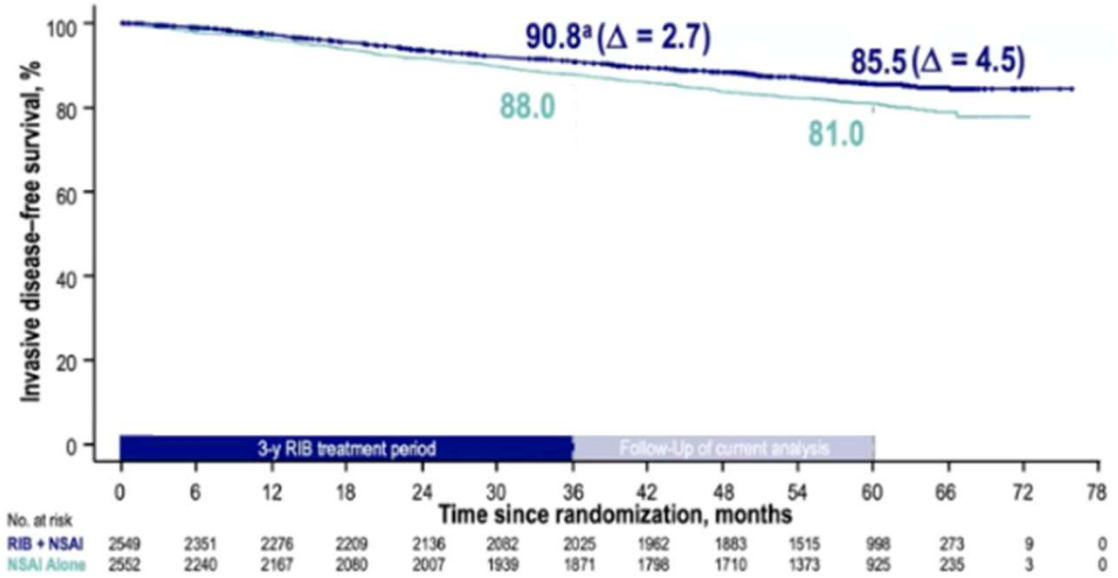
Slamon et al, *Therapeutic Advances in Medical Oncology* 2023

NATALEE- Study Design



Slamon et al, *Therapeutic Advances in Medical Oncology* 2023

iDFS in the ITT Population

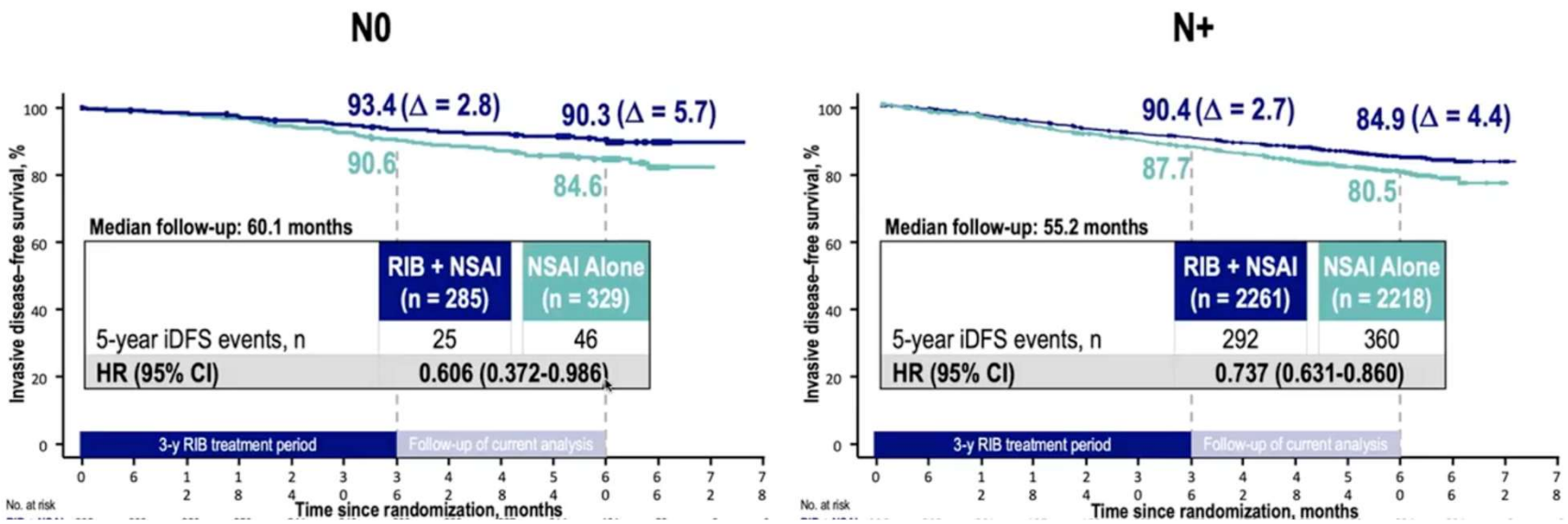


	RIB + NSAI (n = 2549)	NSAI alone (n = 2552)
5-year iDFS events, n	317	407
HR (95% CI)	**0.716 (0.618-0.829)**	
Nominal *P* value (1-sided)[b]	<.0001	

Median Follow up: 55.4 months

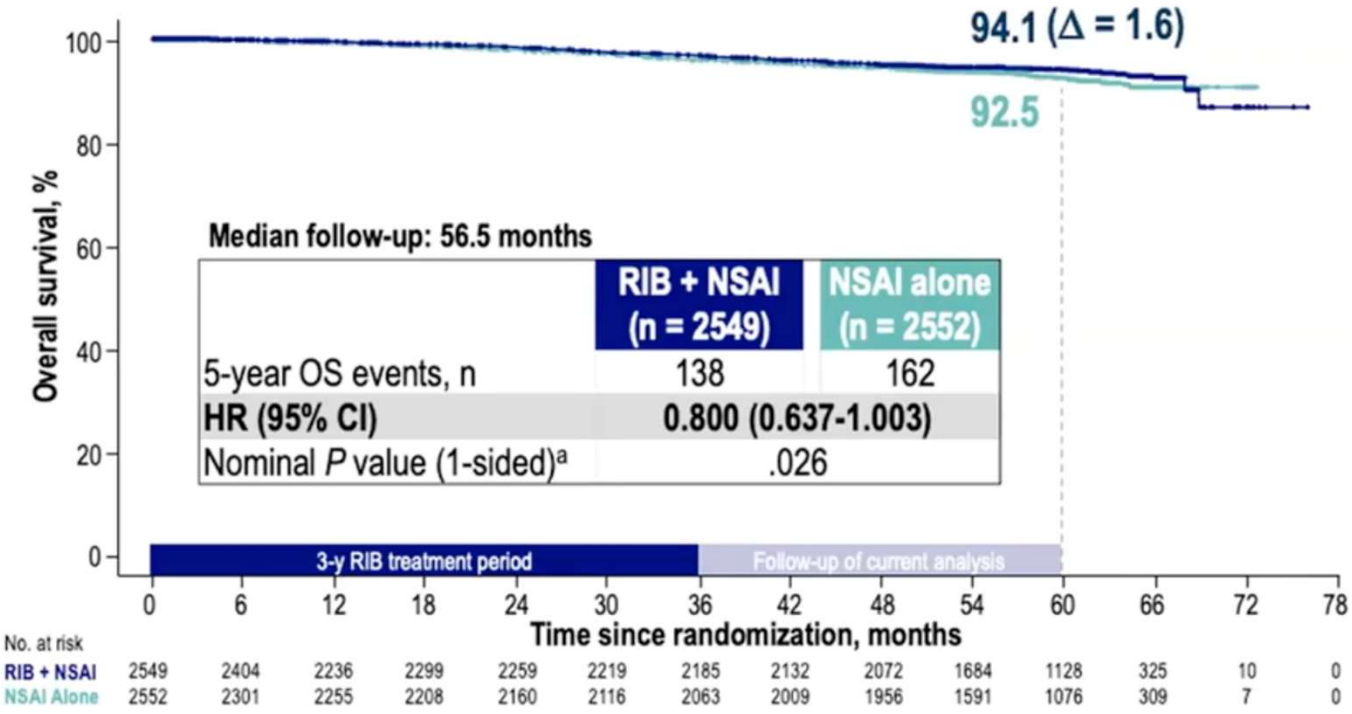
Crown J, et al. ESMO 2025.

iDFS by Nodal Status



Crown J, et al. ESMO 2025.

OS in the ITT Population



Crown J, et al. ESMO 2025.

Which agent should we choose?

	Abemaciclib	**Ribociclib**
Population	High-risk, **node-positive** HR+/HER2- EBC (≥4 nodes OR 1–3 nodes + high-risk features)	**Broader population**: anatomic stage II–III HR+/HER2- (includes some **node-negative high-risk pts**)
Treatment duration	2 years	3 years
Endocrine backbone	AI or tamoxifen ± OFS	Aromatase inhibitor
iDFS benefit	~30–35% relative risk reduction (early and durable separation)	~25% relative risk reduction
Distant relapse-free survival (DRFS)	Significant and sustained improvement	Significant improvement
Overall survival (OS)	**Statistically significant OS benefit**	OS data **immature** (trend only)
Median follow-up (latest)	~7 years	~4–5 years
Key toxicity profile	Diarrhea, fatigue, neutropenia	Neutropenia, QT prolongation, hepatotoxicity
Dose intensity	Continuous dosing	Lower dose (400 mg) vs metastatic setting
Key clinical strength	**Only adjuvant CDK4/6 with proven OS benefit**	**Expands CDK4/6 use beyond very high-risk pts**
Key unresolved question	Optimal patient selection beyond clinical risk	Will OS benefit emerge with longer follow-up?

Patient Case:

- **52yo post-menopausal woman with HR+/HER2- invasive ductal carcinoma s/p lumpectomy + SLNBx.**

- **Pathology:** pT2 (3.2cm), Grade 3, 2/4 positive axillary LN, ER 95%, PR 40%, Ki67 18%, no LVI, Oncotype 34

- **Clinical context:**
  - -- completed adjuvant AC-T; ECOG 0
  - -- PMHx: IBS with baseline loose stools
  - -- strong preference to minimize long-term treatment burden

Patient Case: Polling Question

She is planning to start adjuvant aromatase inhibitor, which adjuvant CDK4/6 strategy would you recommend?

A. Abemaciclib (2 years) + Aromatase Inhibitor

B. Ribociclib (3 years) + Aromatase Inhibitor

C. Aromatase inhibitor alone

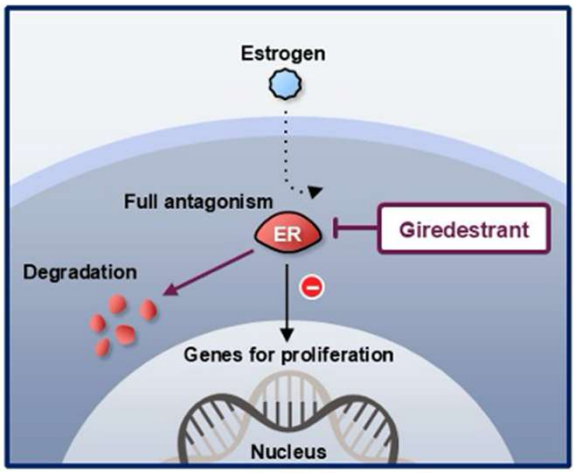
D. Would individualize further (genomic/AI risk tool before deciding)

Outline

- Adjuvant CDK 4/6 inhibitors
  - monarchE
  - NATALEE
- **lidERA Trial — SERD Giredestrant**
- Artificial Intelligence (AI) in the Adjuvant Setting

liDERA Breast Cancer Trial:

Giredestrant vs. standard-of-care endocrine therapy as adjuvant treatment for ER+/HER2- early breast cancer

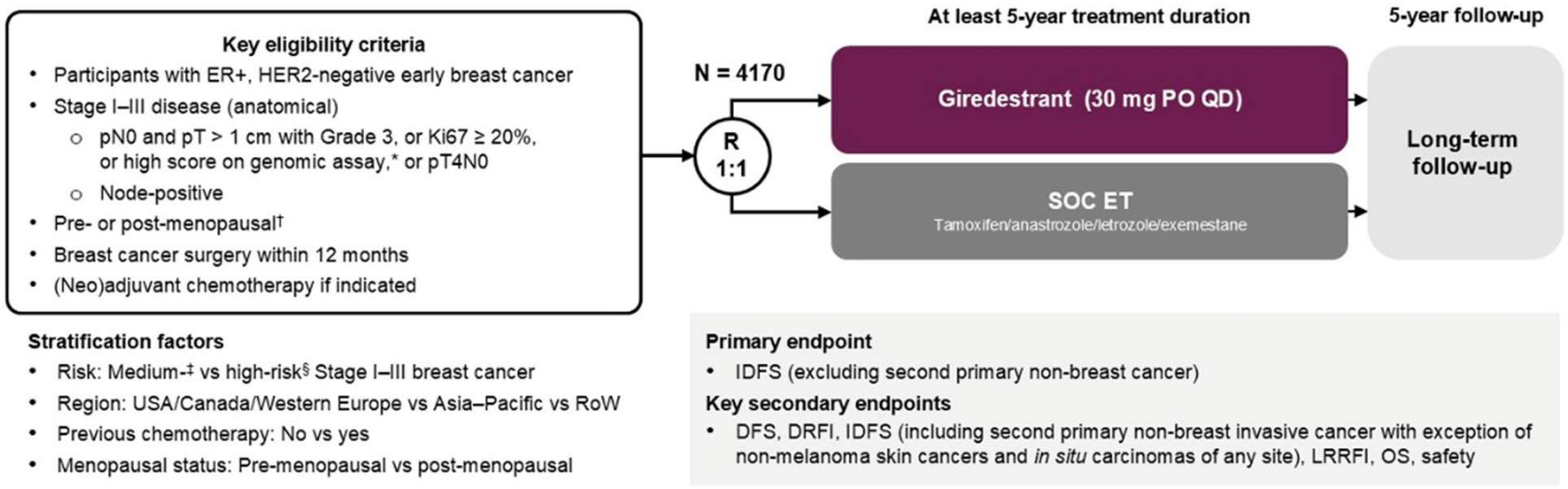


Giredestrant mechanism of action
(selective estrogen receptor antagonist and degrader)

Giredestrant: potent next-generation oral SERD and full ER antagonist, designed to drive deep and sustained inhibition of ER signaling, both ligand dependent and ligand independent

Bardia A, et al. SABCS 2025

liDERA Breast Cancer Trial: Study Design



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Baseline demographics and characteristics

	Giredestrant n = 2084	SOC ET n = 2086
Median age, years (range)	54.0 (22–91)	54.0 (25–89)
Female sex, n (%)	2073 (99.5)	2075 (99.5)
Race, n (%)		
American Indian or Alaska Native	77 (3.7)	62 (3.0)
Asian	461 (22.1)	467 (22.4)
Black or African American	50 (2.4)	50 (2.4)
Other*	263 (12.6)	232 (11.1)
White	1233 (59.2)	1275 (61.1)
Region, n (%)		
Asia–Pacific	544 (26.1)	544 (26.1)
USA/Canada/Western Europe	860 (41.3)	905 (43.4)
Latin America/Africa/Eastern Europe	680 (32.6)	637 (30.5)
Menopausal status, n (%)†		
Pre-menopausal	849 (41.0)	838 (40.4)
Post-menopausal	1220 (59.0)	1236 (59.6)

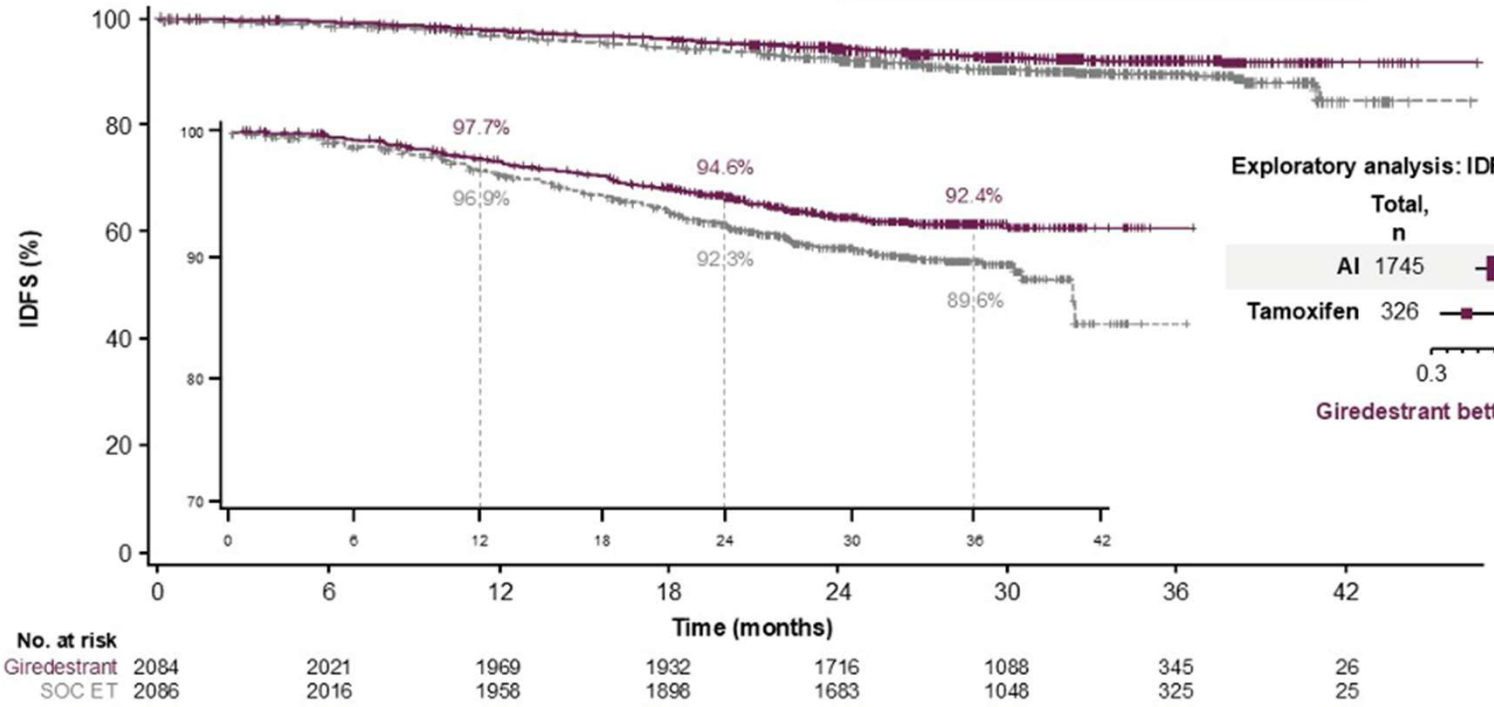
	Giredestrant n = 2084	SOC ET n = 2086
ER status, n (%)‡		
Low-positive (1–10% of cells positive)	45 (2.2)	52 (2.5)
Positive (> 10% of cells positive)	2030 (97.8)	2031 (97.5)
AJCC stage at surgery, n (%)§		
I	254 (12.3)	283 (13.6)
II	1013 (49.0)	950 (45.7)
III	799 (38.7)	844 (40.6)
Nodal status, n (%) on surgical specimen‖		
pN0	449 (21.6)	441 (21.2)
pN1	968 (46.6)	953 (45.7)
pN2–3	662 (31.8)	691 (33.1)
Risk, n (%)		
High	1448 (69.5)	1447 (69.4)
Medium	636 (30.5)	639 (30.6)
Previous chemotherapy, n (%)		
No	396 (19.0)	450 (21.6)
Yes	1688 (81.0)	1636 (78.4)

Baseline demographics and characteristics were balanced

Bardia A, et al. SABCS 2025

Primary Endpoint: IDFS

	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	140 (6.7)	196 (9.4)
Stratified HR (95% CI)	**0.70 (0.57, 0.87); p = 0.0014***	



Exploratory analysis: IDFS by SOC ET

	Total, n	Stratified HR (95% CI)
AI	1745	0.73 (0.58, 0.92)
Tamoxifen	326	0.53 (0.35, 0.80)

0.3 0.8

Giredestrant better | SOC ET better

No. at risk

Giredestrant	2084	2021	1969	1932	1716	1088	345	26
SOC ET	2086	2016	1958	1898	1683	1048	325	25

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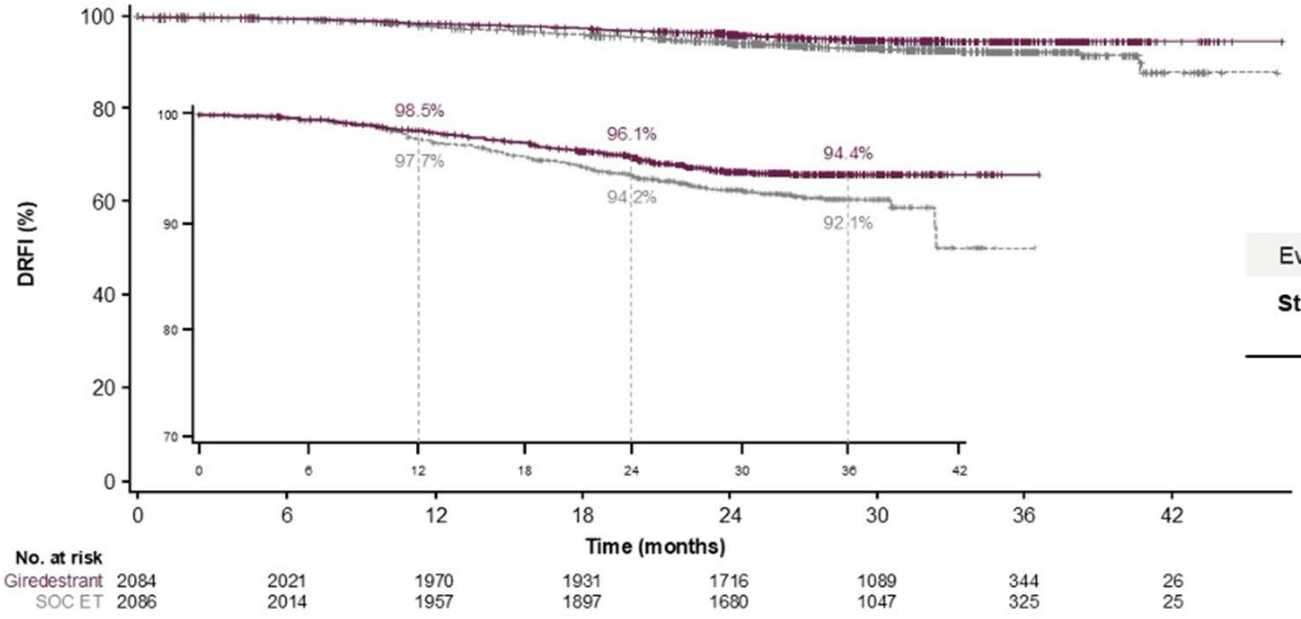
Distant Recurrence-Free Interval

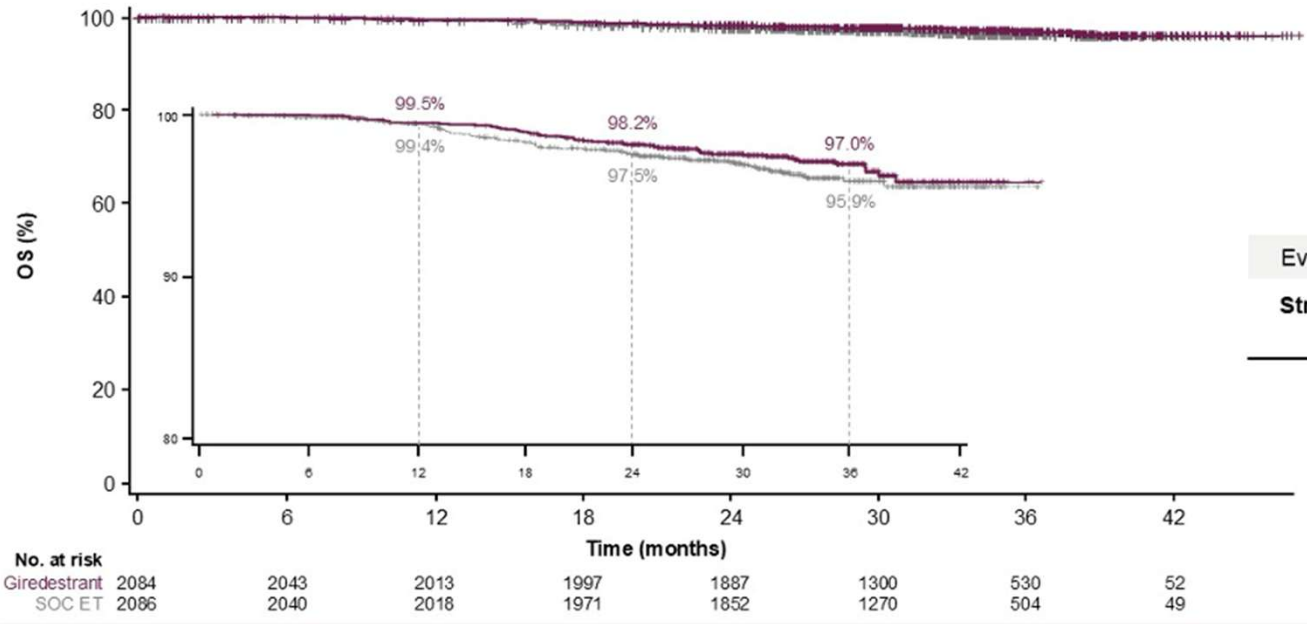


	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	102 (4.9)	145 (7.0)
Stratified HR (95% CI)	**0.69** (0.54, 0.89)	

Median follow-up: 32.3 months

Bardia A, et al. SABCS 2025

Interim Overall Survival



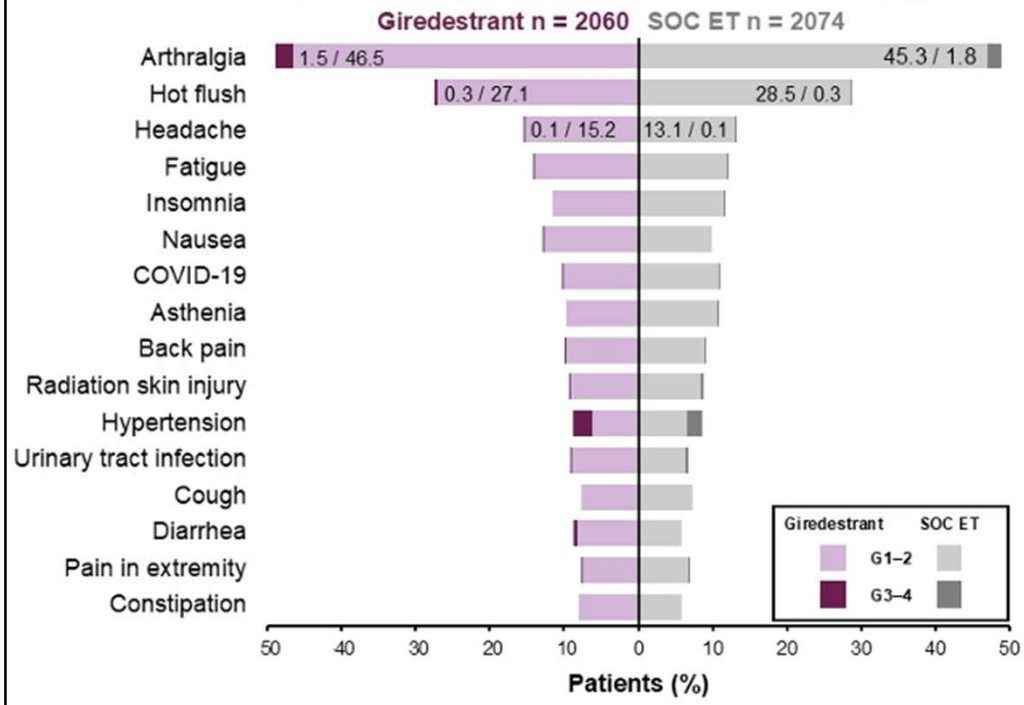
	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	57 (2.7)	71 (3.4)
Stratified HR (95% CI)	**0.79** (0.56, 1.12); p = 0.1863*	

Median follow-up: 32.3 months

- Overall Survival data is immature
- Positive trend was observed
- OS testing will come at future analyses

Bardia A, et al. SABCS 2025

Common TEAEs (≥ 7.5% of patients in either arm at any grade)



Selected AEs

	Giredestrant n = 2060	SOC ET n = 2074
Patients, n (%) with treatment discontinuations due to AEs		
Musculoskeletal disorders	38 (1.8)	92 (4.4)
• Arthralgias (PT)	32 (1.6)	76 (3.7)
Vasomotor disorders	2 (< 0.1)	18 (0.9)
• Hot flush (PT)	1 (< 0.1)	16 (0.8)

	Giredestrant n = 2060			SOC ET n = 2074		
Patients, n (%) with selected AEs by medical concept*						
	G1	**G2**	**G3–4**	**G1**	**G2**	**G3–4**
Bradycardia†	217 (10.5)	15 (0.7)	0	64 (3.1)	2 (< 0.1)	0
Venous thromboembolic events	4 (0.2)	12 (0.6)	2 (< 0.1)‡	3 (0.1)	7 (0.3)	7 (0.3)

Bardia A, et al. SABCS 2025

Conclusions:

- First trial to demonstrate benefit with a novel endocrine therapy in early breast cancer since approval of AI's in 2000s
- Median follow up of 32.3 months: giredestrant improved IDFS compared to SOC endocrine therapy (HR 0.70)
  - 3-year IDFS rates: 92.4% vs 89.6%
- Discontinuation rate of giredestrant was lower compared to SOC endocrine therapy

Considerations:

- Premenopausal patients: require ovarian function suppression (OFS) while on SERDs
  - Some ongoing trials looking at omission of OFS
- Should everyone get giredestrant or restricted to higher risk populations?
- Role of CDK 4/6 inhibitors?
- Biomarker testing/AI to determine those who would benefit the most
- Extended therapy needed and duration of therapy

Outline

- Adjuvant CDK 4/6 inhibitors
  - monarchE
  - NATALEE
- lidERA Trial — SERD Giredestrant
- **Artificial Intelligence (AI) in the Adjuvant Setting**
  - **GS1-08:** Multimodal artificial intelligence (AI) models integrating image, clinical, and molecular data for predicting early and late breast cancer recurrence in TAILORx
  - **RF3-01:** Clinical outcomes of invasive lobular carcinoma (ILC) versus non-lobular breast cancer (NLC) assessed by expert pathologists, an AI CDH1 classifier, and AI-derived tumor microenvironment biomarkers in TAILORx
  - **RF3-07:** A Multimodal-Multitask Deep Learning Model Trained in NSABP B-42 and Validated in TAILORx for Late Distant Recurrence Risk in HR+ Early Breast Cancer

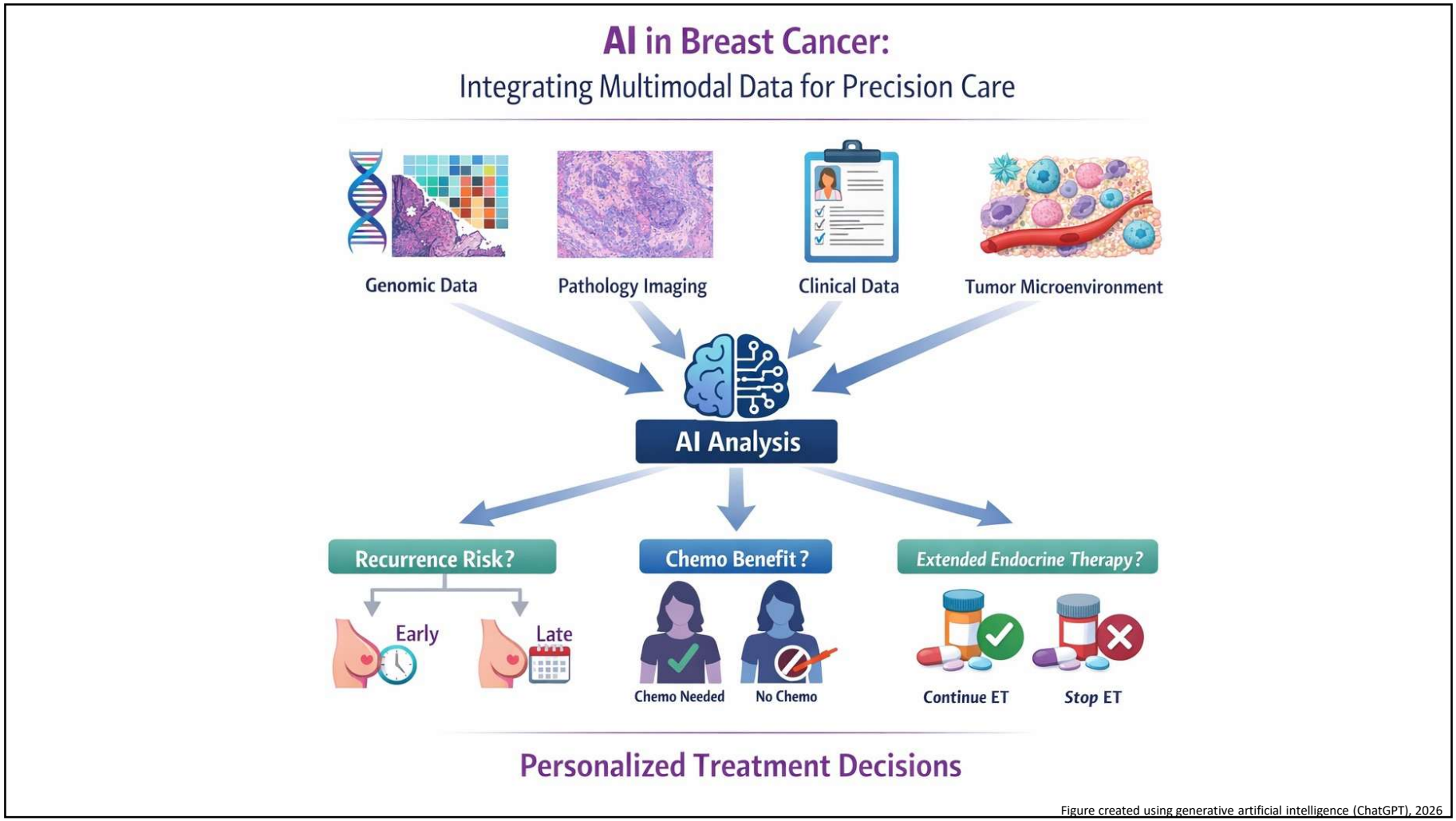
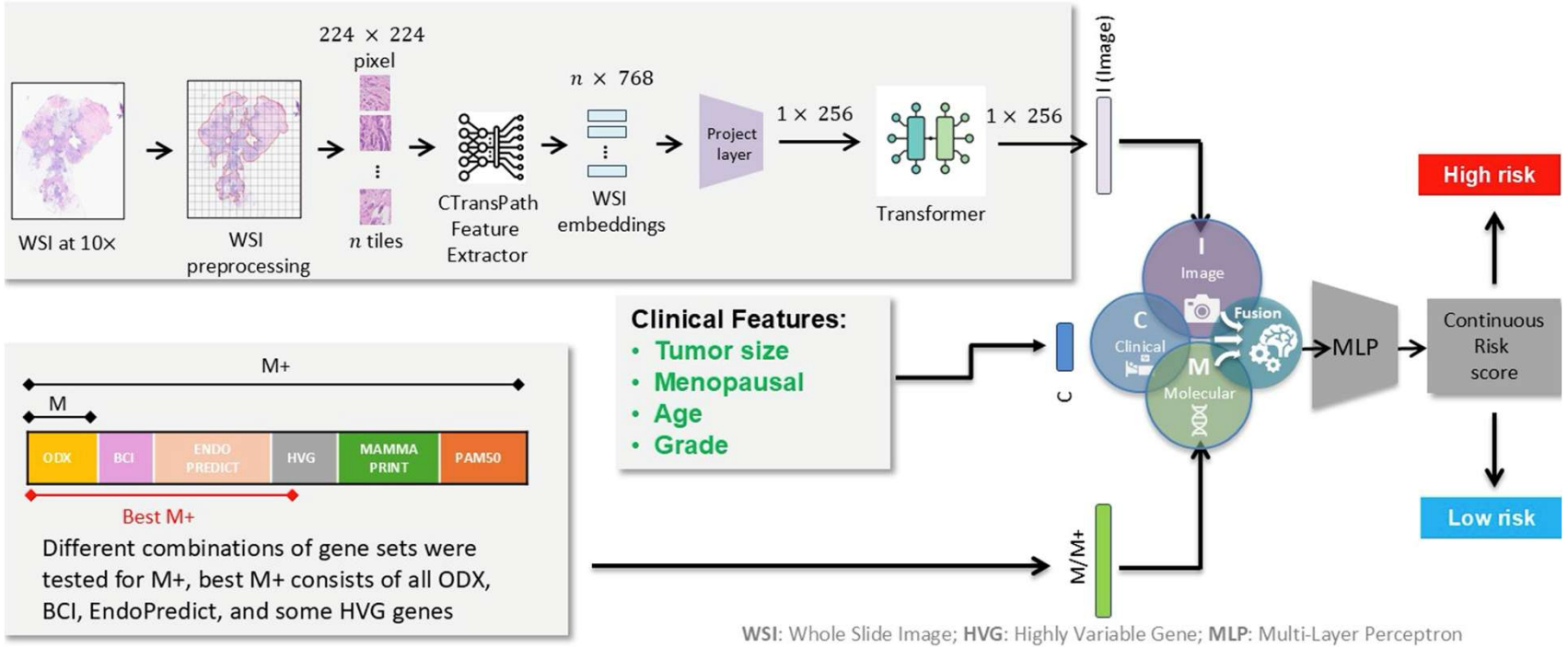


Figure created using generative artificial intelligence (ChatGPT), 2026

GS1-08: Multimodal artificial intelligence (AI) models integrating image, clinical, and molecular data for predicting early and late breast cancer recurrence in TAILORx

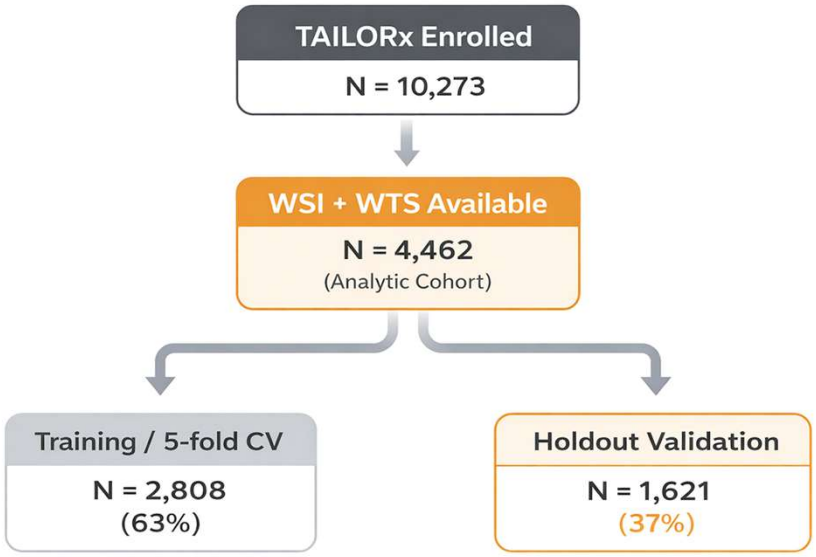
Objective: develop a diagnostic test with better distant recurrence risk prognostication than the Oncotype DX 21-gene RS



WSI: Whole Slide Image; **HVG**: Highly Variable Gene; **MLP**: Multi-Layer Perceptron

Sparano J, et al. SABCS 2025

GS1-08: Multimodal artificial intelligence (AI) models integrating image, clinical, and molecular data for predicting early and late breast cancer recurrence in TAILORx



- **Training/5-fold Cross Validation Set**
  - Used to build the ICM+ model
  - Learn which features matter and how much weight to give them
  - Model learns patterns that associate features with:
    - Whether recurrence occurred
    - When it occurred (time-to-event)
- **Holdout Validation Set**
  - Completely excluded from model development
  - Not used for feature selection, weighting, or tuning
  - The final, locked ICM+ model was applied to them **without seeing their outcomes**
  - Only **after predictions were generated** were those predictions compared with:
    - Actual recurrence status
    - Time to recurrence

Sparano J, et al. SABCS 2025

GS1-08: Multimodal artificial intelligence (AI) models integrating image, clinical, and molecular data for predicting early and late breast cancer recurrence in TAILORx

Dataset	Outcome	Oncotype DX	ICM+
Training / 5-fold CV (n = 2,806)	Overall distant recurrence (15 years)	0.617	**0.705**
	Late distant recurrence (>5 years)	0.518	**0.656**
Holdout validation (n = 1,621)	Overall distant recurrence	0.631	**0.733**
	Late distant recurrence	0.527	**0.705**

C-index (concordance index) to quantify performance:

0.5 ——— 0.6 ——— 0.7 ——— 1.0
Chance Moderate Good Perfect

0.5 = no better than chance
>0.70 = good discrimination
1.0 = perfect prediction

Sparano J, et al. SABCS 2025

Key Take-Home Points

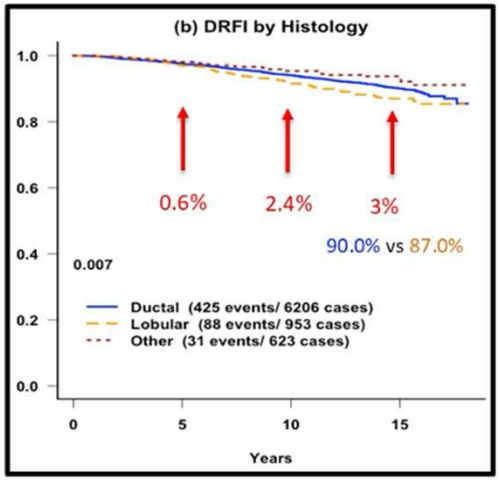
- **Multimodal AI improves recurrence prediction**
  Integrating pathology images, clinical, and molecular data outperforms single-modality tools

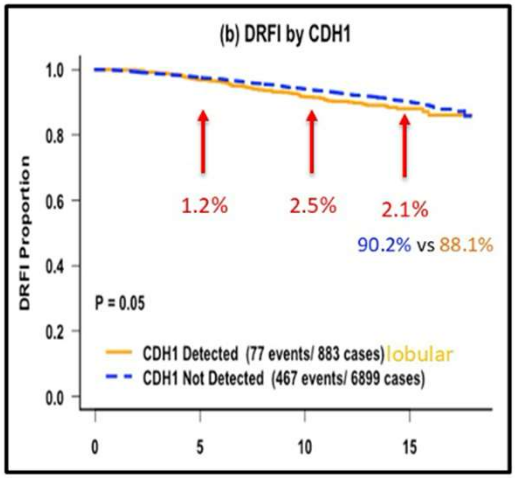
- **Outperformed OncotypeDx RS**
  Supports AI as a complementary tool to genomic assays for long-term risk stratification

- **Strong performance for late recurrence risk**
  Addresses a major unmet need in HR+/HER2- early breast cancer

Sparano J, et al. SABCS 2025

RF3-01: Clinical outcomes of invasive lobular carcinoma (ILC) versus non-lobular breast cancer (NLC) assessed by expert pathologists, an AI CDH1 classifier, and AI-derived tumor microenvironment biomarkers in TAILORx



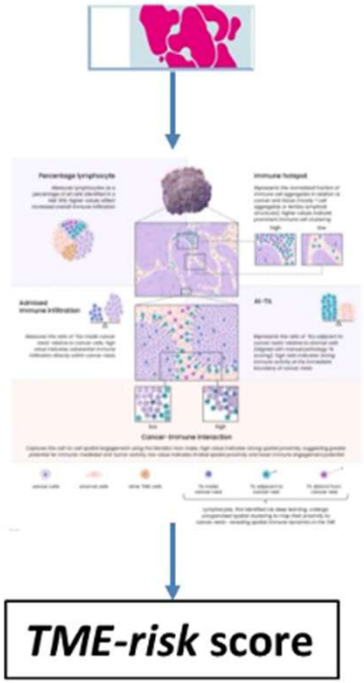


- Both centralized pathology review and the CDH1-AI classifier demonstrated that ILC has consistently higher risk of recurrence than NLC between years 5-15
- Curves start to separate at 5 years
- In TAILORx, most patients received only 5 years of endocrine therapy

- Discordances between pathology histology and AI are low (6.8%)
  - 44% were AI-CDH1+ aberrant and called non-lobular by pathologist
  - 54% were AI- CDH1 normal and called lobular by pathologist

Salgado R, et al. SABCS 2025

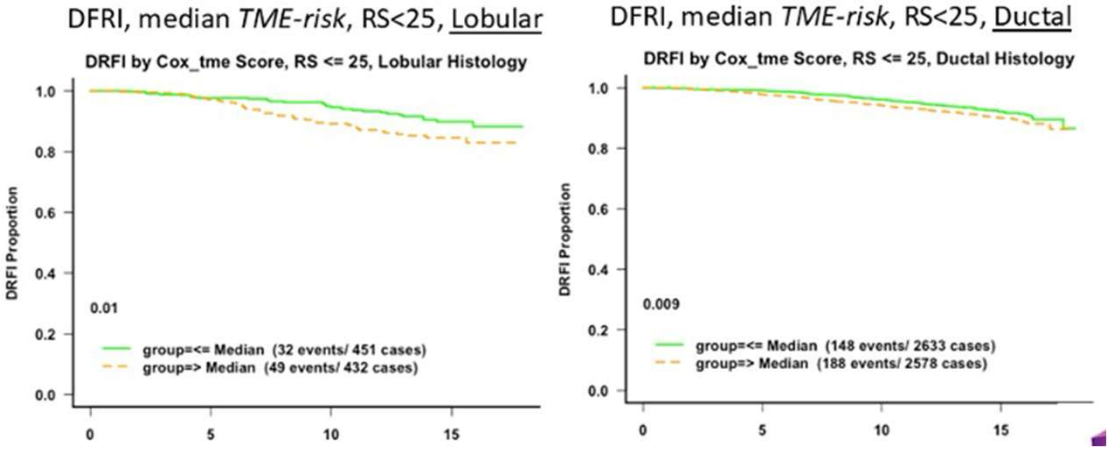
RF3-01: Clinical outcomes of invasive lobular carcinoma (ILC) versus non-lobular breast cancer (NLC) assessed by expert pathologists, an AI CDH1 classifier, and AI-derived tumor microenvironment biomarkers in TAILORx



Panel of TME biomarkers such as TILs, spatial TIL patterns, and degree of cancer-fibroblast contact

***TME-risk* score**

Clinical outcomes using a zero-shot AI model for TME biomarkers



- Within Oncotype <25 patients (low genomic risk), TME-risk score further stratifies recurrence risk in both ductal and lobular subtypes
- Within patients that have a low genomic risk, may find a subset who based on TME biomarkers, are NOT low risk

Salgado R, et al. SABCS 2025

Key Take-Home Points

- Lobular breast cancer carries higher late recurrence risk than non-lobular disease
- An AI derived TME analysis provides independent risk stratification in addition to OncotypeDx, particularly in RS <25
- Findings may have implications for duration of endocrine therapy in selected ILC patients despite low genomic risk

Salgado R, et al. SABCS 2025

RF3-07: A Multimodal-Multitask Deep Learning Model Trained in NSABP B-42 and Validated in TAILORx for Late Distant Recurrence Risk in HR+ Early Breast Cancer

B-42 Translational Cohort: 2271 **Training/Evaluation: 5-fold cross validation**

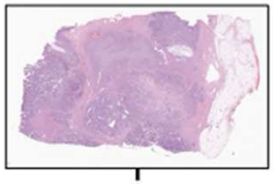


IMAGE ONLY MODEL

AUXILIARY TASK
Lowest BMD T-score

RISK SCORE

IMAGE + CLINICAL MODEL

CLINICAL FEATURES
- Nodal status
- Surgery
- Age

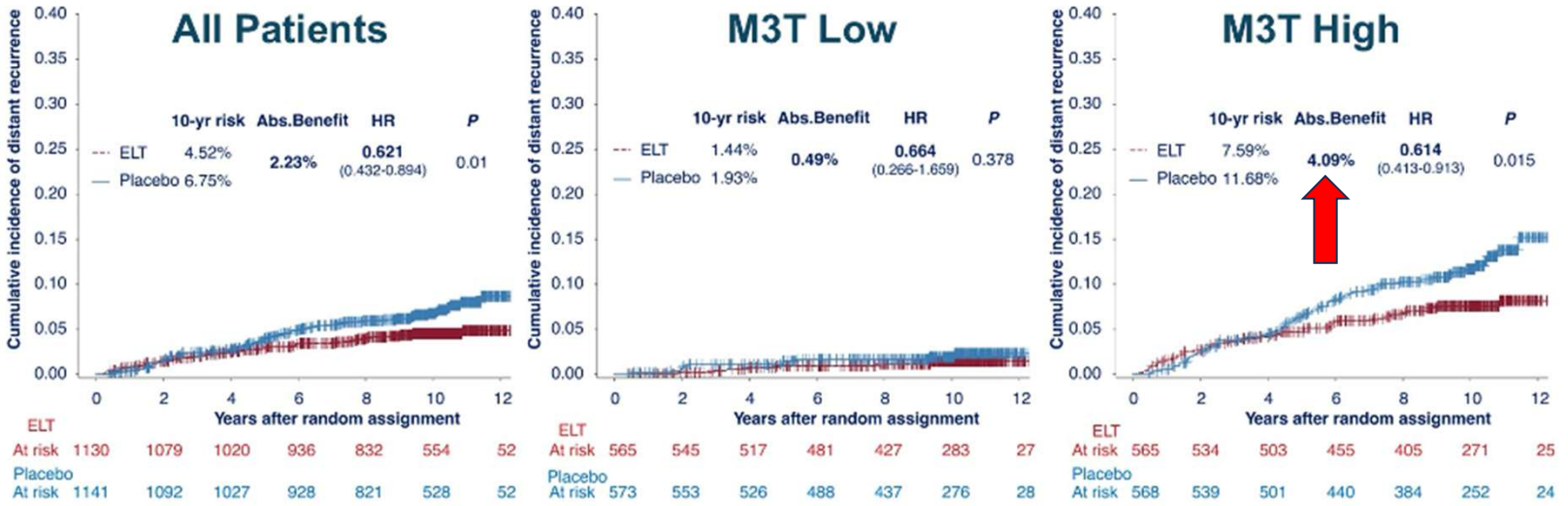
In Multimodal-multitask architecture, BMD T-score is not used as input. Instead, there is an auxiliary task that predicts T-score, along with a risk score, in the training set.

T-score is not needed for test cases.

MODEL INPUT
- **Image only model input: H&E**
- **Multimodal model: H&E + clinical**
- **Multimodal-multitask (M3T) model: H&E + clinical as input and T-Score as additional target variable**

Mamounas E, et al. SABCS 2025

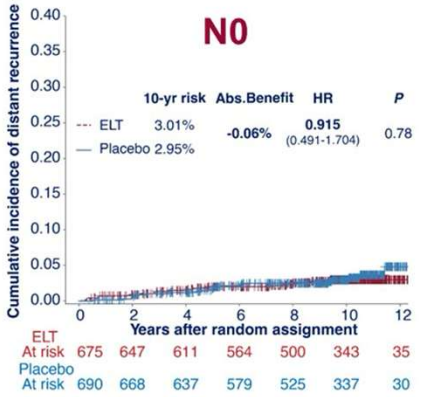
M3T Model Suggests a Subgroup More Likely to Benefit from Extended Letrozole Therapy

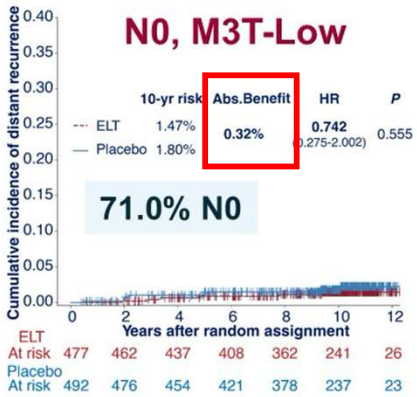


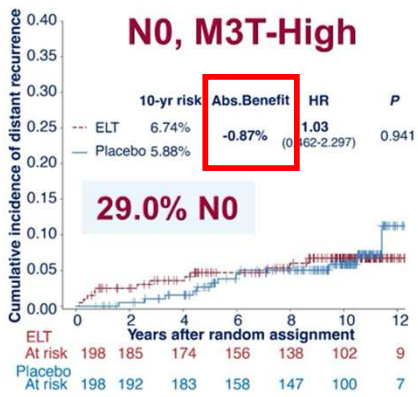
Mamounas E, et al. SABCS 2025

M3T Reclassifies 18.7% N+ patients as Low Risk and 29% N0 Patients as High Risk

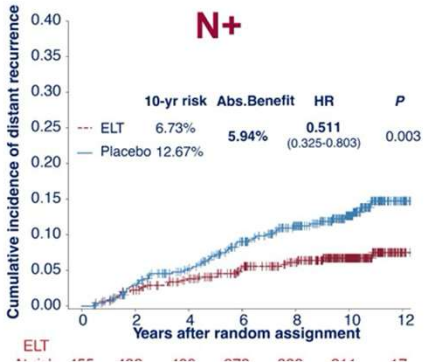
Path. Node Negative

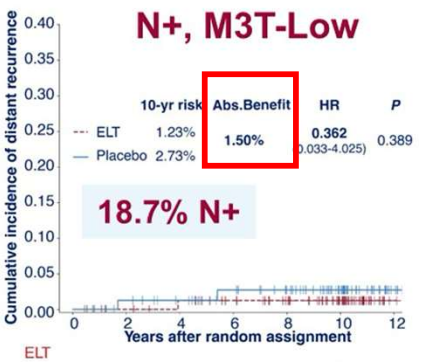


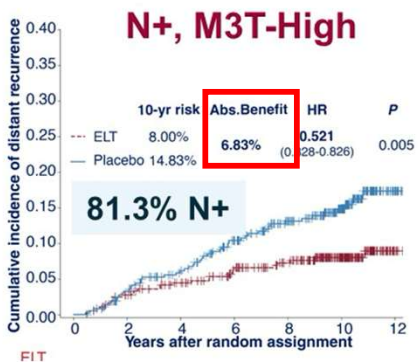




Path. Node Positive





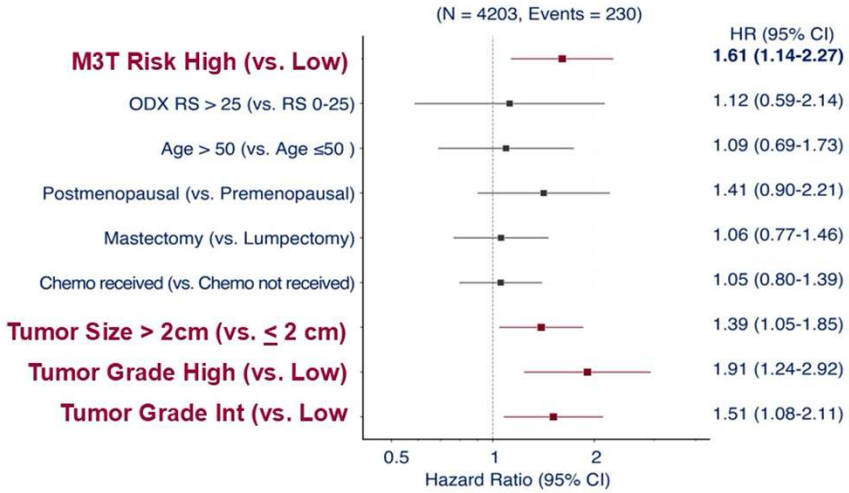


Mamounas E, et al. SABCS 2025

External Validation of the M3T Model in TAILORx: Prediction of Risk of Late Distant Recurrence

N=4,300

Late DR (LDR): Patients with ≥ 4.5 yrs of ET and disease-free at 5 yrs



- M3T risk label was an independent predictor of distant recurrence along with tumor size and grade

Mamounas E, et al. SABCS 2025

Key Take-Home Points

- M3T model identified low-risk patients, unlikely to obtain meaningful benefit from extended endocrine therapy
- Potential treatment guidance beyond standard clinicopathological factors
- External validation in TAILORx confirmed independent late DR prognostication

Salgado R, et al. SABCS 2025

What These 3 Abstracts Collectively Show:

- AI consistently:
  - Improves prognostic accuracy
  - Adds biologic insight beyond genomics alone
- Strong signals for:
  - Late recurrence prediction
  - Biologic tumor classification
- AI is moving from:
  - "Exploratory" → **decision-support**
- Potential impact on:
  - CDK4/6 inhibitor selection
  - Extended endocrine therapy
  - Chemotherapy de-escalation

SABCS 2025 firmly positions multimodal AI as a complementary layer to genomics: enhancing precision across prognosis, prediction, and long-term risk assessment in HR+ breast cancer

Final Thoughts:

Early HR+ breast cancer management is no longer one-size-fits-all.

The future lies in combining better drugs (CDK4/6 inhibitors, SERDs) with better decision tools (AI) to deliver the right intensity, for the right patient, for the right duration.

National Comprehensive Cancer Network®

Neoadjuvant/Adjuvant Treatment of Early-Stage Breast Cancer with SABCS Updates

Triple-Negative Early-Stage Breast Cancer

Kay T. Yeung, MD, PhD

UC San Diego Moores Cancer Center

Where We Are in 2025: Goals and Open Questions

- Stage II–III TNBC: neoadjuvant chemoimmunotherapy is the backbone
- Persistent risk remains for residual disease → need better escalation and better de-escalation
- Two unmet needs SABCS 2025 addressed:
  (1) optimize neoadjuvant backbone (how much does platinum add?)
  (2) personalize escalation/de-escalation (MRD + biology)

SABCS 2025 Highlights: Early-Stage TNBC

Practice-informing study

- RF2-02 (Felsteim): carbo pooled pCR/EFS

Biomarker (MRD/ ctDNA) studies

- RF4-03 (Balic): WES-informed MRD
- RF3-05 (Cunningham): tissue-free ctDNA
- PD7-10 (Loi): ctDNA dynamics + EFS
- RF2-01 (Holtschmidt): Ki67/TILs in residual disease
- RF3-06 (Badve): EA1131: TILs + intrinsic subtypes in residual disease

Novel regimens and survivorship

- RF5-02 (Mayer): TBCRC 056 neoadjuvant niraparib + dostarlimab
- PD7-07 (McArthur): Peri-operative ipilimumab/nivolumab + cryoablation
- PD7-11 (Sharma): ovarian function after neoadjuvant pembrolizumab

Neoadjuvant Therapy for Stage II-III TNBC

- KEYNOTE-522 regimen is currently the standard of care
- The therapeutic benefit of carboplatin to neoadjuvant therapy remained not well defined

RF2-02: Pooled analysis of the BrighTNess, CALBG 40603, and GeparSixto (Felsheim BM, *et al*)

Pooled Analysis of the BrighTNess, CALGB 40603, and GeparSixto

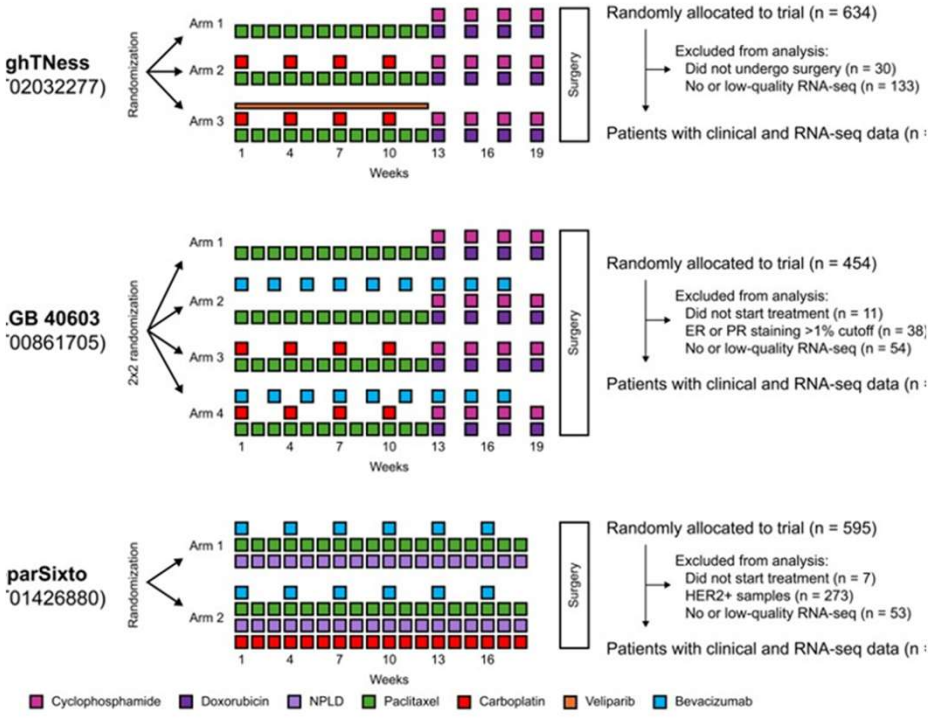
3 randomized study testing the addition of carboplatin to neoadjuvant chemotherapy in early-stage TNBC

N=1084 patients

Primary objective:

- **Evaluate pCR rate, EFS, OS**

Examine predictive value of published gene signature

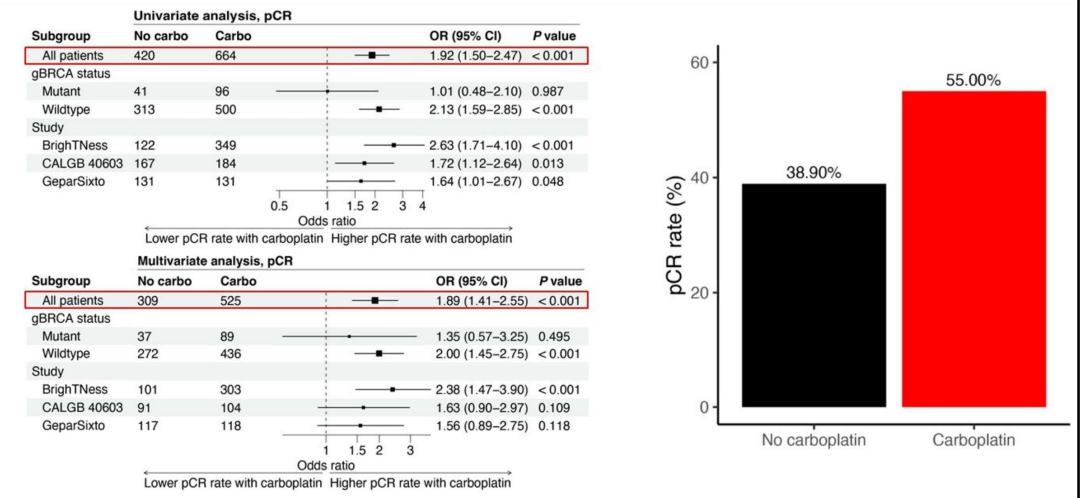


Felsheim BM, et al. SABCS 2025; RF2-02.

What Does Carboplatin Add to Neoadjuvant Chemo?

- pCR improves substantially with carboplatin:
  - 55% vs 38.9%
- Subgroup nuance:
  - pCR gain is most evident in gBRCA-wildtype; no clear pCR increase in gBRCA-mutated subset.
- Multivariate analysis included age, cT, cN, tumor grade, and gBRCA1/2mut as covariates

Take-home point: This reinforces carboplatin as a meaningful pCR driver, with genotype nuance.



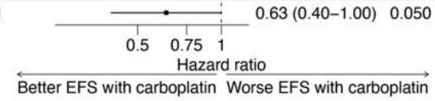
Felsheim BM, et al. SABCS 2025; RF2-02.

Does Carboplatin Improve Long-Term Outcomes?

In the pooled dataset, neoadjuvant carboplatin is associated with better EFS

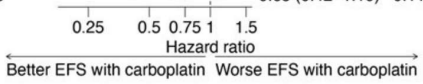
Univariate analysis, EFS

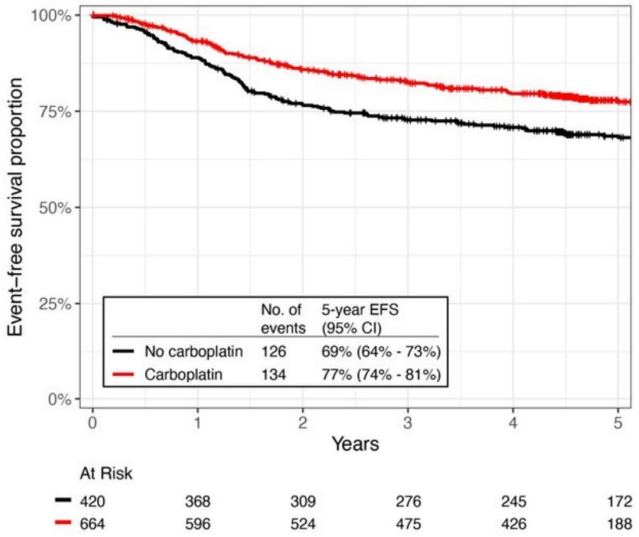
Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	420	664	0.70 (0.55–0.89)	0.003
gBRCA status				
Mutant	41	96	0.50 (0.25–1.00)	0.050
Wildtype	313	500	0.73 (0.55–0.96)	0.024
Study				
BrighTNess	122	349	0.58 (0.38–0.88)	0.010
CALGB 40603	167	184	0.86 (0.59–1.26)	0.439
GeparSixto	131	131	0.63 (0.40–1.00)	0.050



Multivariate analysis, EFS

Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	310	526	0.71 (0.54–0.93)	0.014
gBRCA status				
Mutant	37	89	0.37 (0.18–0.79)	0.010
Wildtype	273	437	0.77 (0.57–1.03)	0.079
Study				
BrighTNess	101	303	0.56 (0.36–0.88)	0.012
CALGB 40603	92	105	0.97 (0.59–1.60)	0.912
GeparSixto	117	118	0.68 (0.42–1.10)	0.113





OS immature

Felsheim BM, et al. SABCS 2025; RF2-02.

MRD/ctDNA and RD Biomarker Studies

- **RF4-03** (Balic): NSABP B-59/GeparDouze: tumor-informed WES ctDNA MRD substudy
- **RF3-05** (Cunningham): c-TRAK-TN: “tissue-free” ctDNA detection (Guardant Reveal) with relapse lead time
- **PD7-10** (Loi): NeoN: 3-yr EFS + ultrasensitive tumor-informed SV-ctDNA dynamics on neoadj carbo/taxol + nivolumab
- **RF2-01** (Holtschmidt): Pooled 9 GBG/AGO-B trials: Ki67 + TILs in residual disease after NACT
- **RF3-06** (Badve): EA1131: TILs in residual disease + intrinsic subtypes

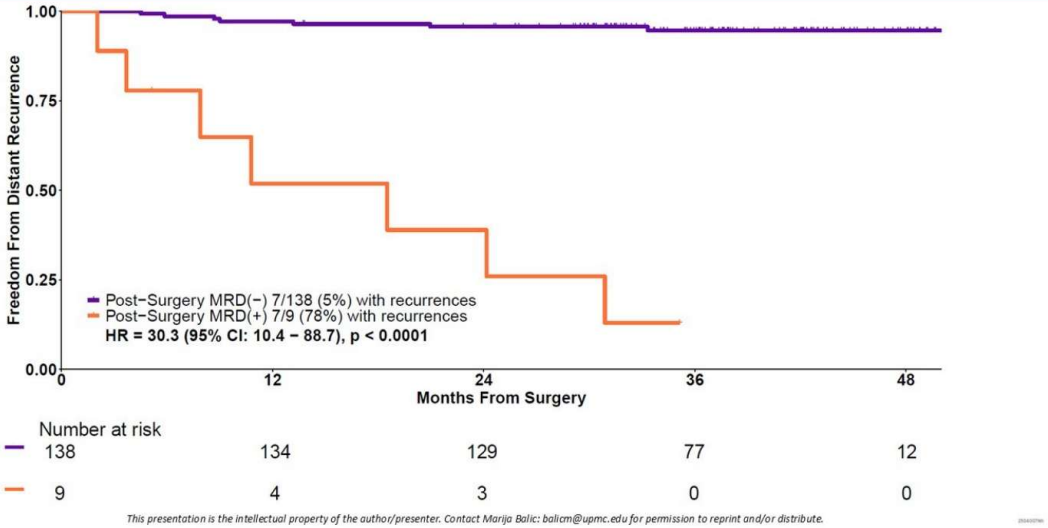
Post-Surgery ctDNA is a Powerful Risk Stratifier

NSABP B59 GeparDouze substudy

- Whole Exome Sequencing (WES)-informed MRD assay in eTNBC treated with NAT ± atezolizumab.
- Post-surgery MRD+ was uncommon (~single digits %) but:
  - relapse in **~78%** of ctDNA+ vs **~5%** of ctDNA−
  - **HR = 30.3** for DRFI.

Take-home point: Post-op ctDNA positivity is essentially a ‘red-flag’.

Primary analysis of DRFI by MRD status post-surgery



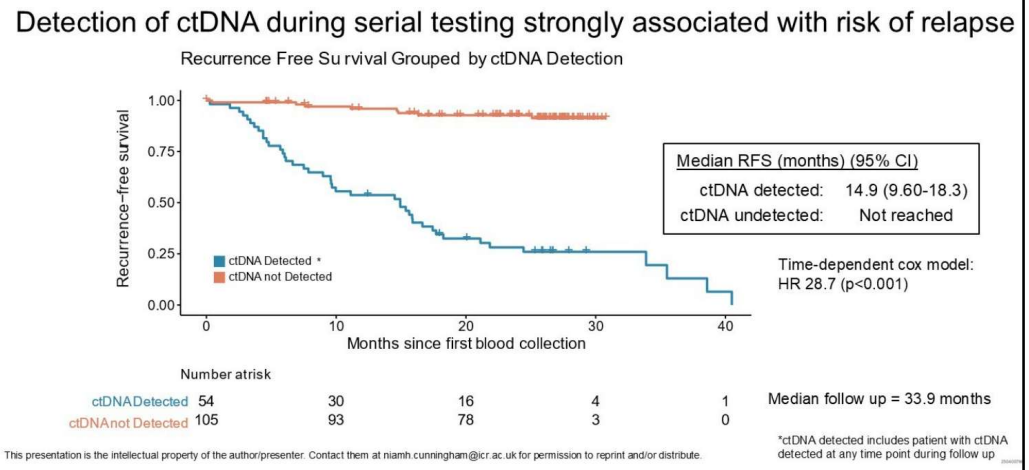
Balic M, et al. SABCS 2025; RF4-03.

Tissue-Free ctDNA May Broaden Access and Improve Lead-Time

c-TRAK-TN

- Tissue-free approach improves practicality (no tumor tissue required)
- Strong association with recurrence:
  - ctDNA detected → median RFS ~14.9 months, vs not reached if undetected time-dependent HR ~28.7
- Tissue-free detected more and sometimes earlier than tumor-informed ddPCR:
  - median time from first detection to relapse ~7.8 months (lead-time window).

Take-home point: This strengthens the case for MRD-triggered intervention trials—but detection ≠ proof that early treatment improves OS



Cunningham N, et al. SABCS 2025; RF3-05.

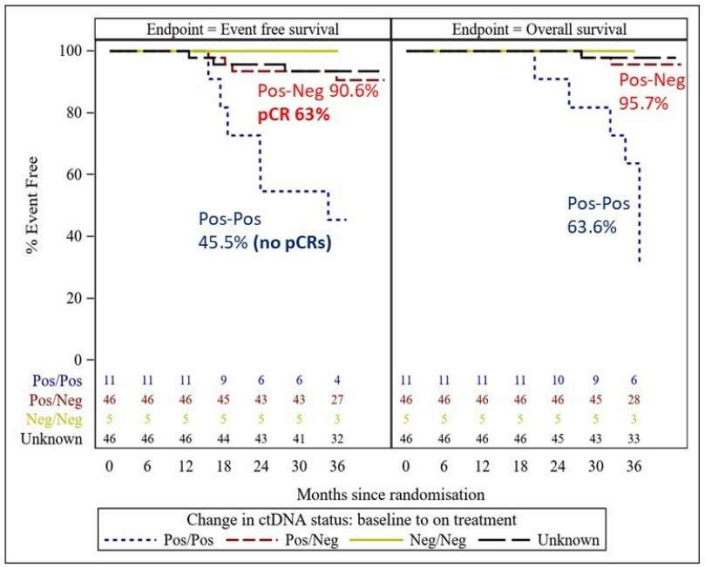
ctDNA Clearance Identifies ‘Good’ vs ‘High-Risk’ Trajectories

NeoN study: short neoadjuvant carbo/taxane + nivolumab strategy; updated 3-yr EFS/OS.

- Overall outcomes look strong (~high-80s% 3-yr EFS overall).
- ctDNA dynamics during study:
  - ctDNA cleared → excellent (90.6% 3yr EFS)
  - ctDNA persists → much worse (45.7% 3yr EFS)

Take-home point: On-treatment ctDNA clearance is a plausible ‘adaptive’ biomarker for escalation vs de-escalation strategies.

ctDNA dynamics and prognosis: baseline to T1



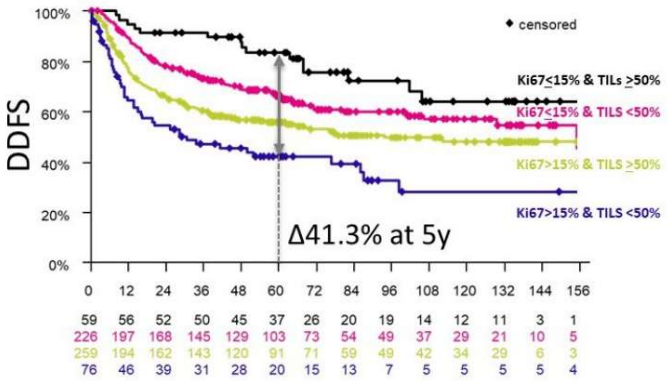
Loi S, et al. SABCS 2025; PD7-10.

Escalation Beyond ‘RCB’ Alone: Ki67 + TILs

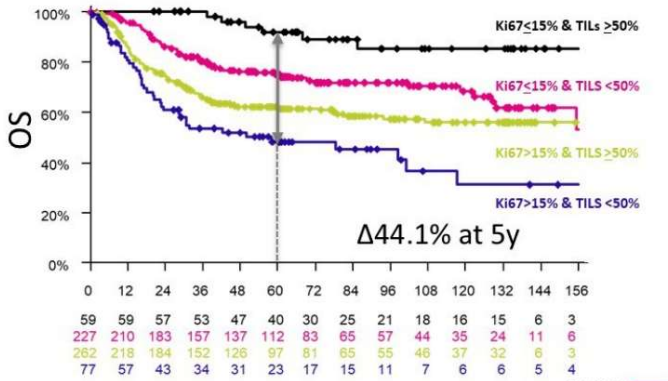
Residual tumors from 9 neoadjuvant **GBG/AGO** studies

- Gepar-Trio, Quattro, Quinto, Sixto, Septo, Octo, Nuevo, Ola, X
- 640 available tumors out of total of 3017 pts with eTNBC

	Events/n	5y DDFS	HR (95% CI)
Ki67≤15% & TILs ≥50%	15/59	83.7% (74.5-94.1)	Reference
Ki67≤15% & TILS <50%	83/226	66.3% (60.1-73.1)	1.66 (0.96-2.89) p=0.07
Ki67>15% & TILS ≥50%	120/259	55.8% (49.9-62.4)	2.35 (1.37-4.03) p=0.002
Ki67>15% & TILS <50%	45/76	42.4% (32.2-55.8)	3.62 (2.00-6.52) p<0.0001



	Events/n	5y OS	HR (95% CI)
Ki67≤15% & TILs ≥50%	6/59	92.1% (84.9-99.9)	Reference
Ki67≤15% & TILS <50%	62/227	75.0% (69.3-81.2)	3.12 (1.35-7.21) p=0.008
Ki67>15% & TILS ≥50%	101/262	61.5% (55.6-67.9)	4.77 (2.09-10.91) p=0.0002
Ki67>15% & TILS <50%	40/77	48.0% (37.4-61.7)	7.57 (3.19-17.94) p<0.0001



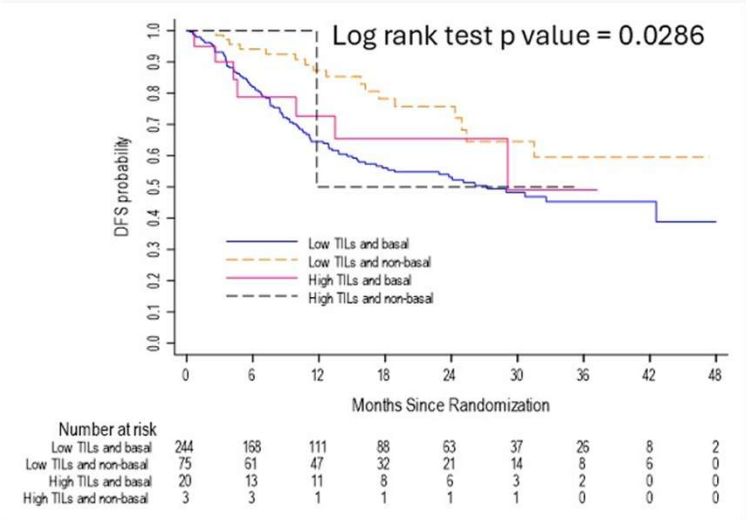
AGO-B BREAST STUDY GROUP

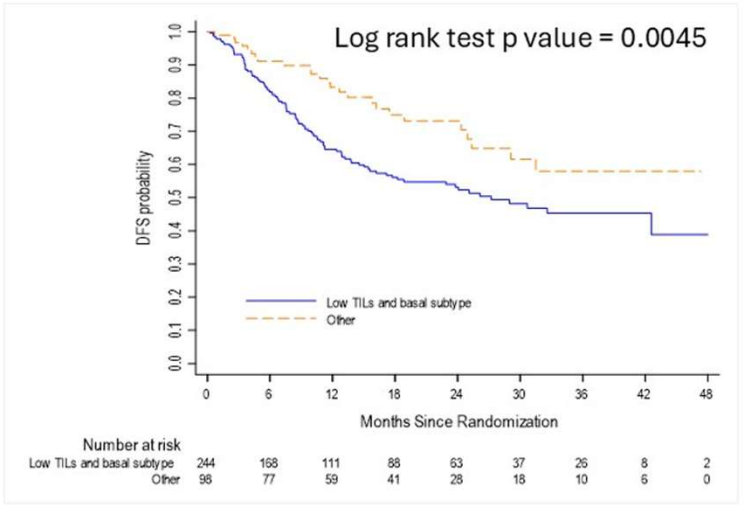
GBG GERMAN BREAST GROUP

Holtschmidt J, et al. SABCS 2025; RF2-01.

Escalation Beyond ‘RCB’ Alone: TILs + Basal/Non-Basal

EA1131: platinum vs capecitabine for TNBC with residual disease (*JCO* 2021, PMID 34092112)





Badve SS, et al. SABCS 2025; RF3-06.

Patients with residual tumors that were basal subtypes + low TILs have the worst iDFS compared to the other subgroups

→ Reinforces biologic heterogeneity in TNBC
→ Residual disease is not one entity: immune context and subtype biology should shape escalation strategies

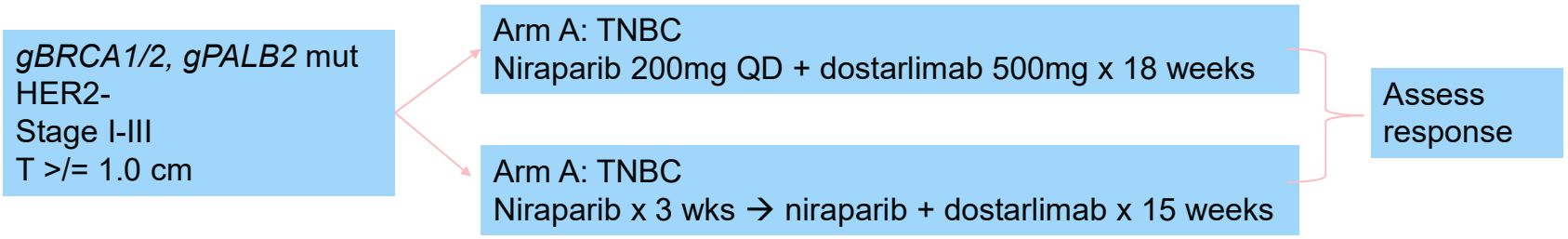
Novel Regimens

- **RF5-02** (Mayer): TBCRC 056: neoadjuvant niraparib + dostarlimab in gBRCA/gPALB2 TNBC cohorts
- **PD7-07** (McArthur): Peri-operative ipilimumab/nivolumab + cryoablation (HR–/HER2– resectable): 3-yr EFS

PARPi + anti-PD1 for *gBRCA/gPALB2* TNBC

- Preclinical data support synergy between PARPi and immunotherapy
- PARPi → intratumoral activation of cGAS/STING pathway → CD8+ T cell recruitment → sensitizing *gBRCA*mut cancers to immunotherapy

TBCRC-056 Study Design



Primary Objectives: pCR and change in stromal TILs from baseline to cycle 2

Mayer EL, et al. SABCS 2025; RF5-02.

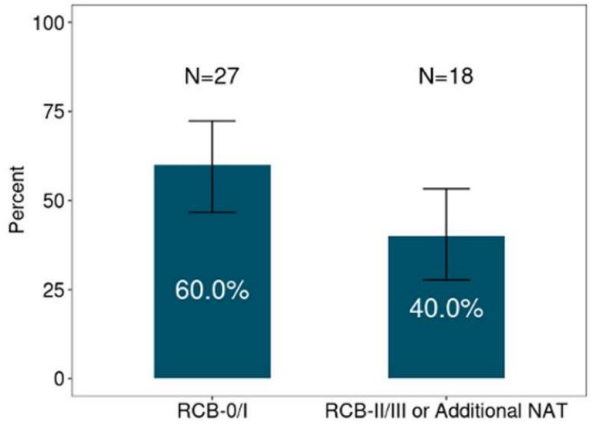
TBCRC-056 TNBC Cohort Result

Response at Surgery

Pathologic Response	N	%
pCR / RCB-0	**23**	**50.0 (90% CI 37.1 – 62.9)**
Arm A	**11/22**	**50.0**
Arm B	**12/24**	**50.0**
RCB-I	4	8.7
RCB-II	5	10.9
RCB-III	2	4.3
Unable to calculate	1	2.2
Additional NAT	11	23.9
Total	**46**	**100.0**

pCR rates the same in BRCA1 vs BRCA2

RCB Response

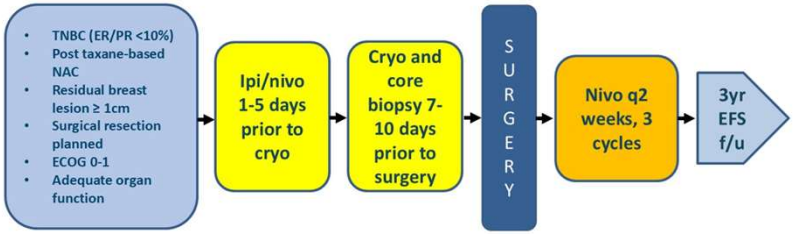


N=45, excluding case with RCB unable to calculate

→ Small study but an important de-escalation signal in germline carriers
→ needs validation and long-term outcomes

Mayer EL, et al. SABCS 2025; RF5-02.

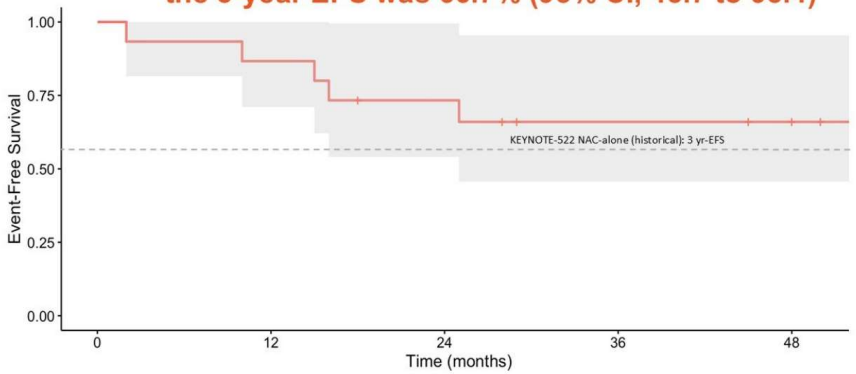
ICI + cryoablation for TNBC residual disease



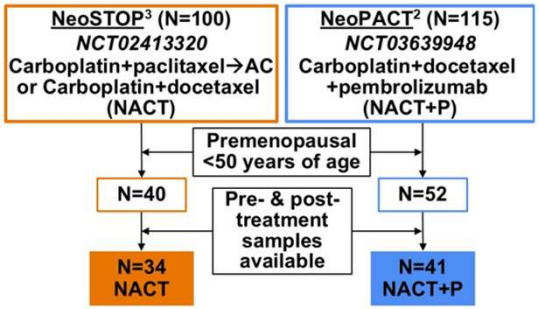
Characteristic, n(%)	N=15
Age	
Median (range) – yr	55 (32–75)
<65 yr – no. (%)	10 (66.7)
Race/Ethnicity – no. (%)	
White/non-Hispanic	10 (66.7)
White/Hispanic	2 (13.3)
Black or African American	1 (6.7)
Asian	2 (13.3)
Residual Tumor Size, median (range) – cm	3 (1.1–7.5)
Neoadjuvant Chemotherapy	
Taxane + Anthracycline	4 (26.7)
Taxane + Platinum	10 (66.7)
Taxane-only	1 (6.7)

McArthur HL, et al. SABCS 2025; PD7-07.

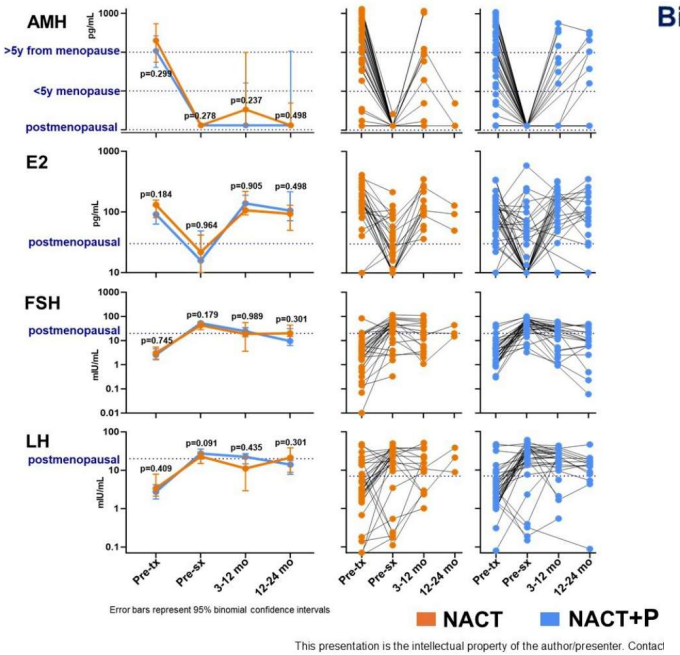
At a median follow-up of 49.5 months (data cutoff: June 1, 2025), the 3-year EFS was 66.7% (95% CI, 45.7 to 95.4)

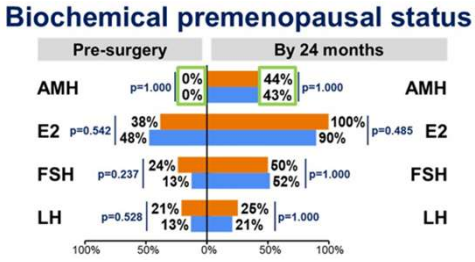


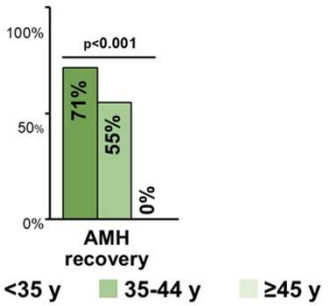
Survivorship: Does Pembrolizumab Affect Ovarian Function



N=75 patients <50 years of age and self-reported premenopausal with available pre-treatment and at least one serial post-treatment serum samples were included in this analysis







→ Pembrolizumab did not appear to worsen AMH recovery beyond chemotherapy in NeoSTOP vs NeoPACT

Sharma P, et al. SABCS 2025; PD7-11.

Take-Home Points

1. Carboplatin meaningfully increases pCR and is associated with improved EFS in pooled RCT data.
2. ctDNA MRD after NAT/surgery is a ‘high-precision’ risk tool: rare positivity, but extremely high relapse risk.
3. On-treatment dynamics (ctDNA clearance, immune context) can segment patients for escalation vs de-escalation trials.
4. Next wave: biologic tailoring (TNBC subtypes, TIL/Ki67, MRD) + chemo-sparing regimens for defined genotypes.

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To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

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