Hot topics in the management of early breast cancer

What's new in 2023: treatment tailoring and optimization

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Luminal

Escalating adjuvant therapy

- Incorporation of CDK4/6-inhibitors: NATALEE, update of MONARCH-E

De-escalating therapy

- TAM-01: Low-dose tamoxifen for prevention
- POSITIVE: Interrupting ET to attempt pregnancy

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HER2+

De-escalating therapy using biomarkers
- PHERGAIN trial (PET-CT)
- Utility of HER2DX in treatment tailoring

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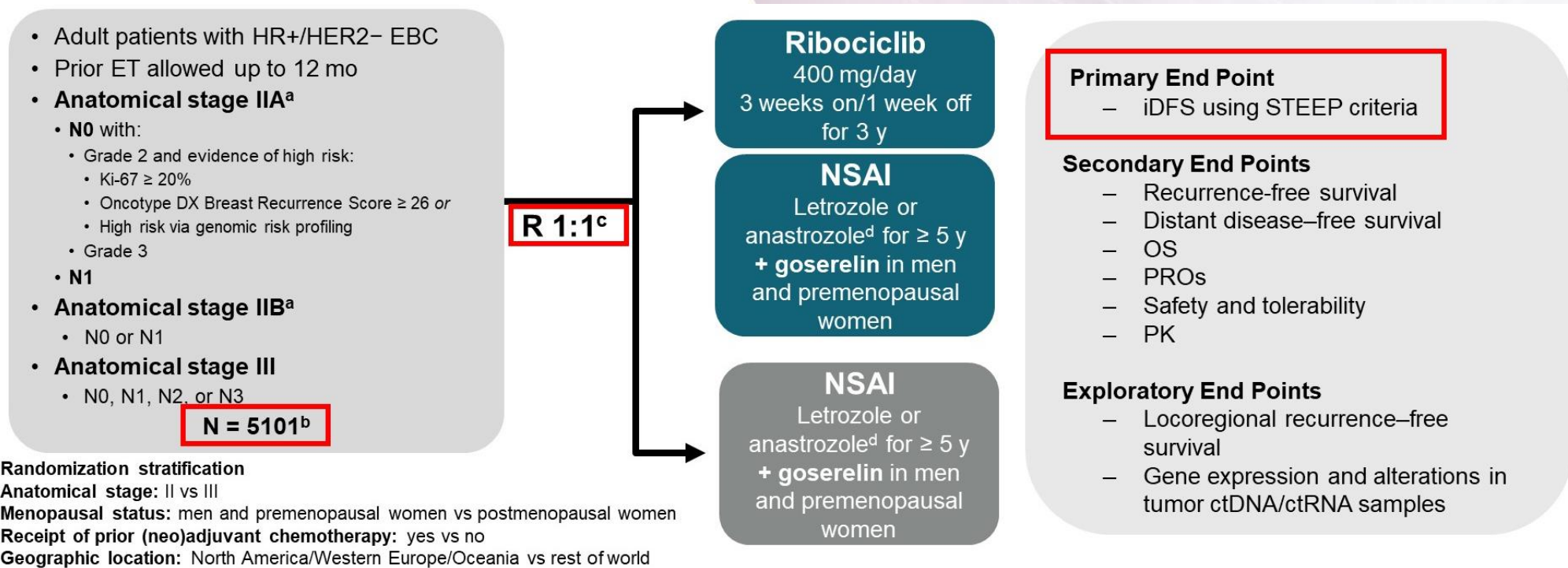- Utility of HER2DX in treatment tailoring

Triple negative

De-escalating therapy
- NeoPACT: Omitting anthracyclines
- Coming soon: Using TILs to de-escalate therapy
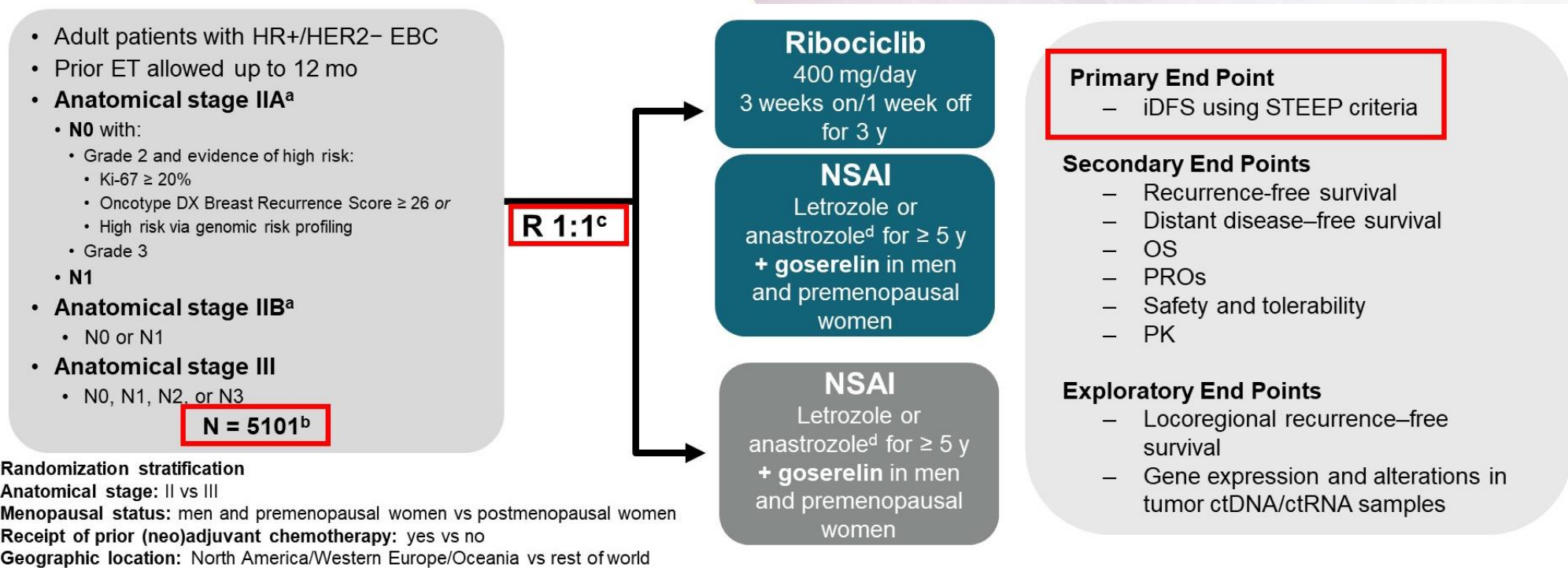
Luminal Breast Cancer: Escalating adjuvant therapy

NATALEE Trial

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA[a]**
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB[a]**
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or
anastrozole[d] for ≥ 5 y
+ goserelin in men
and premenopausal
women

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Primary End Point
  - iDFS using STEEP criteria

Secondary End Points
  - Recurrence-free survival
  - Distant disease–free survival
  - OS
  - PROs
  - Safety and tolerability
  - PK

Exploratory End Points
  - Locoregional recurrence–free survival
  - Gene expression and alterations in tumor ctDNA/ctRNA samples

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

Slamon D et al. ASCO 2023

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- 56% post-menopausal
- Stage: IIA 20%, IIB 20%, III 60%
- Nodal status: N0 28%, N1 41%, N2/3 19%

- Prior ET 71%
- Prior (neo)adjuvant CT 88%

Slamon D et al. ASCO 2023

Luminal Breast Cancer: Escalating adjuvant therapy

NATALEE Trial: Patient disposition

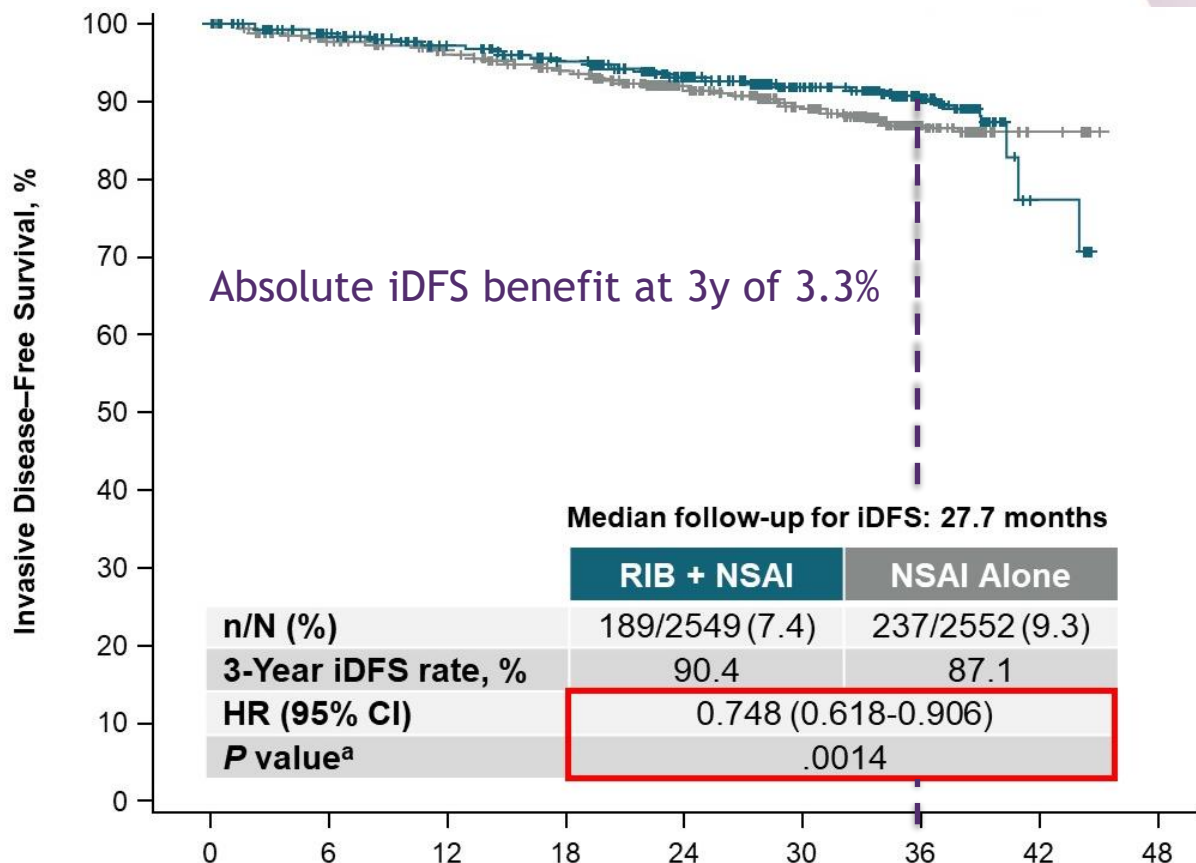### Median follow-up of 34.0 months (minimum, 21 months)[a]

Parameter, n %	RIB + NSAI n = 2549	NSAI alone n = 2552
Patients treated	2526 (99)	2442 (96)
Patients with treatment ongoing[b]	1984 (78)	1826 (72)
Patients who discontinued NSAI	542 (21)	617 (24)
Primary reason for treatment discontinuation (NSAI)[c]		
Adverse Event	118 (5)	105 (4)
Patient/Physician decision	256 (10)	296 (12)
Disease relapse	142 (6)	186 (7)
Other[d]	13 (0.5)	15 (0.6)
Lost to follow-up	8 (0.3)	12 (0.5)
Death[e]	5 (0.2)	3 (0.1)
Patients who completed ribociclib treatment		
≥2 years (including ongoing)	1449 (57)	-
Completed 3 years RIB	515 (20)	-
Primary reason for early discontinuation of RIB[f]		-
Adverse Event	477 (19)	-

NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Randomization to data cutoff of January 11, 2023. [b] In the RIB + NSAI arm, the treatment is considered ongoing if the patient is continuing either study treatment. [c] All components of treatment are discontinued if NSAI is discontinued. [d] Includes protocol deviations. [e] Causes of death in the RIB + NSAI arm were COVID-19 pneumonia, pulmonary embolism, and traffic accident, and in patients who had previously discontinued RIB but remained on NSAI, the causes of death were cardiac arrest and brain edema; for patients in the NSAI alone arm, the causes of death were myocardial infraction, sepsis, and unknown. [f] RIB could be discontinued early due to AEs, all other reasons for discontinuations would require both components be discontinued and are captured above.
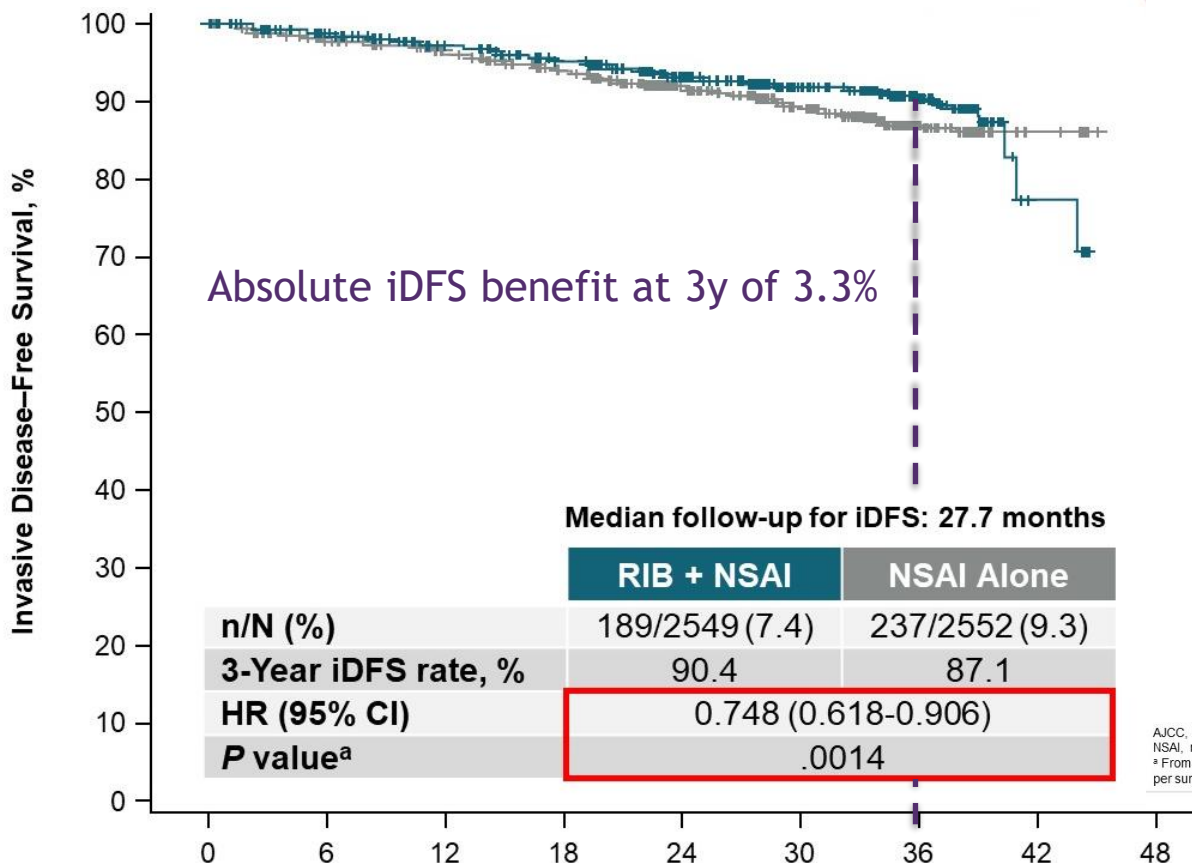
Luminal Breast Cancer: Escalating adjuvant therapy

NATALEE Trial: Second interim analysis (426 iDFS events) with a median follow-up of 27.7 months

Absolute iDFS benefit at 3y of 3.3%

Median follow-up for iDFS: 27.7 months

	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

No. at risk

	0	6	12	18	24	30	36	42	48
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

Slamon D et al. ASCO 2023

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Subgroup	RIB + NSAI n = 2549	NSAI Alone n = 2552	HR	(95% CI)
Menopausal status				
Men and premenopausal women	71/1126	93/1132	0.722	(0.530-0.983)
Postmenopausal women	118/1423	144/1420	0.781	(0.613-0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525-1.103)
Stage III	140/1528	172/1512	0.740	(0.592-0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610-1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486-0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598-0.955)
No	62/725	80/751	0.774	(0.556-1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591-0.974)
Rest of world	78/986	98/987	0.757	(0.562-1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328-1.846)
Grade 2	102/1460	125/1432	0.749	(0.577-0.973)
Grade 3	61/684	78/702	0.776	(0.555-1.085)
Ki-67 status[a]				
Ki-67 ≤ 20%	76/1199	95/1236	0.801	(0.593-1.083)
Ki-67 > 20%	82/920	105/938	0.746	(0.559-0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341-1.165)
N1-N3	173/2261	208/2219	0.771	(0.630-0.944)

AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Favors RIB + NSAI Favors NSAI alone

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Luminal Breast Cancer: Escalating adjuvant therapy

NATALEE Trial: Safety

AESIs, %	RIB + NSAI n = 2524		NSAI Alone n = 2444	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Neutropenia[a]	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	25.4	8.3	10.6	1.5
QT interval prolongation[c]	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis[d]	1.5	0	0.8	0.1
Other clinically relevant AEs,%				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%

- Most of the AE discontinuations of RIB occurred early in treatment
 - Median time of these discontinuations was 4 months

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

Slamon D et al. ASCO 2023

Luminal Breast Cancer: Escalating adjuvant therapy

Monarch-E Trial: iDFS at the second OS interim analysis (Lancet Oncol 2023)

Median follow-up 42 months (IQR 37–47), all patients have completed abemaciclib
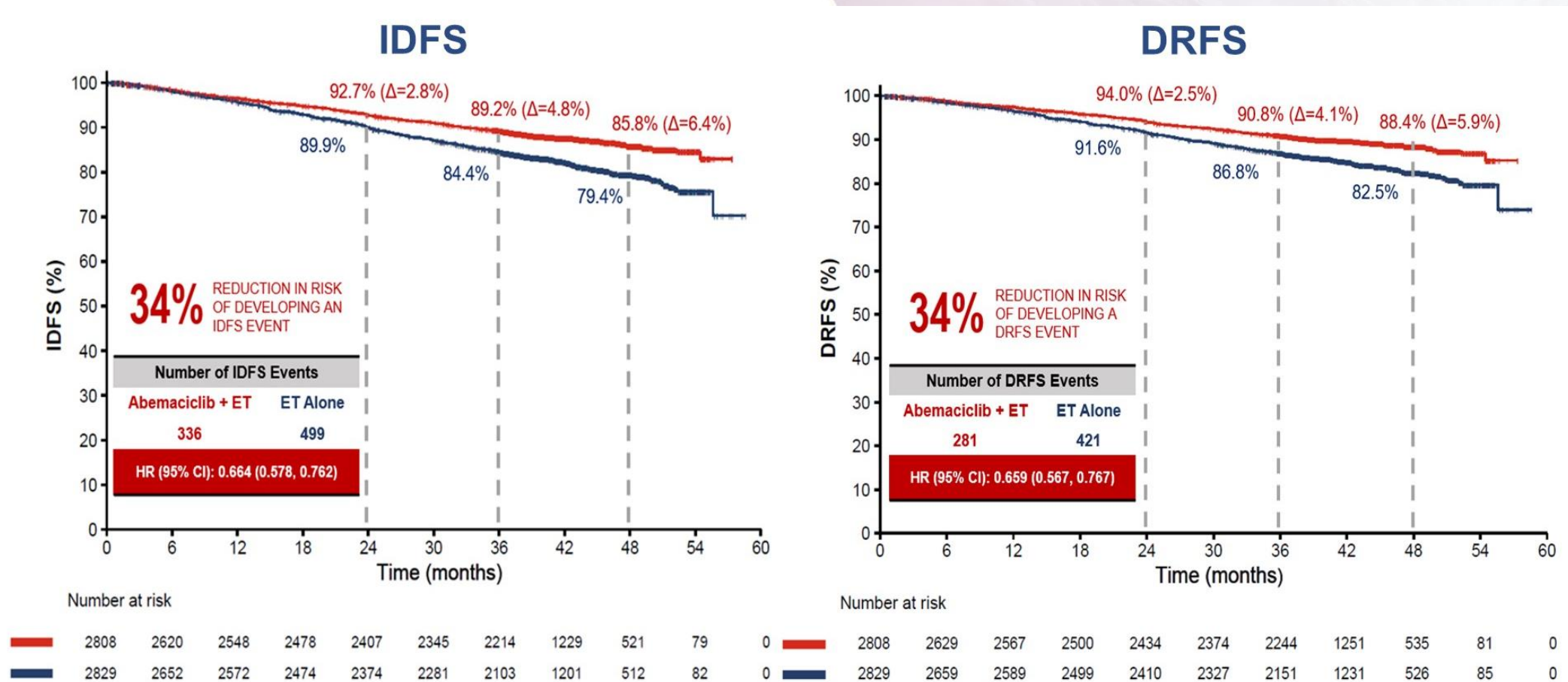
OS: HR 0.929 (95% CI 0.748 1.153), Log-rank p=0.50

Johnston S et al. Lancet Oncol 2023; 24: 77–90

Luminal Breast Cancer: Escalating adjuvant therapy

Monarch-E Trial: iDFS by age

	IDFS			DRFS		
	ITT	**<65**	**≥65**	**ITT**	**<65**	**≥65**
Events/N						
Abemaciclib + ET	336/2808	270/2371	66/437	281/2808	230/2371	51/437
ET alone	499/2829	414/2416	85/413	421/2829	353/2416	68/413
HR (95% CI)	0.664 (0.578, 0.762)	0.646 (0.554, 0.753)	0.767 (0.556, 1.059)	0.659 (0.567, 0.767)	0.647 (0.548, 0.764)	0.748 (0.520, 1.077)
Interaction p-value	NA	0.35		NA	0.49	
4-year rate, %						
Abemaciclib + ET	85.8	86.5	82.0	88.4	88.8	86.1
ET alone	79.4	79.8	76.8	82.5	82.6	81.5
Absolute benefit	6.4	6.7	5.2	5.9	6.2	4.6

Consistent benefit of abemaciclib in iDFS and DRFS independently of age

Hamilton E et al. ASCO 2023

Luminal Breast Cancer: Escalating adjuvant therapy

Monarch-E Trial: toxicity and dose modifications by age

| AE, % | Grade | Abemaciclib + ET | | |
		Overall n=2791	<65 n=2361	≥65* n=430
Any AE	Any	98	98	99
	G≥3	50	49	54
Clinically relevant AEs				
Diarrhea	G1	45	46	37
	G2	31	31	30
	G3	8	7	12
Fatigue	G1	23	23	21
	G2	15	14	20
	G3	3	2	6
Neutropenia	G1/2	26	27	22
	G≥3	20	20	19
ALT increase	G1/2	10	10	7
	G≥3	3	3	3
VTE	Any	3	2	3
	G≥3	1	1	1
ILD	Any	3	3	3
	G≥3	<1	<1	<1

*Patients ≥75 years had higher rates of grade 3 diarrhea and grade 2/3 fatigue

Similar AE profile independently of age

Luminal Breast Cancer: Escalating adjuvant therapy

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	G≥3	<1	<1	<1

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Abemaciclib dose adjustments due to AEs, %	Abemaciclib + ET		
	Overall n=2791	<65 n=2361	≥65* n=430
Interruptions	62	60	68
Reductions	44	42	55
Discontinuations	18	15	38
Discontinuations without prior dose reductions	10	8	19

*Patients ≥75 years had higher rates of abemaciclib dose adjustments and discontinuations due to AEs

Similar AE profile independently of age

Higher proportion of dose adjustments (including discontinuations) in older patients

Hamilton E et al. ASCO 2023

Luminal Breast Cancer: Escalating adjuvant therapy

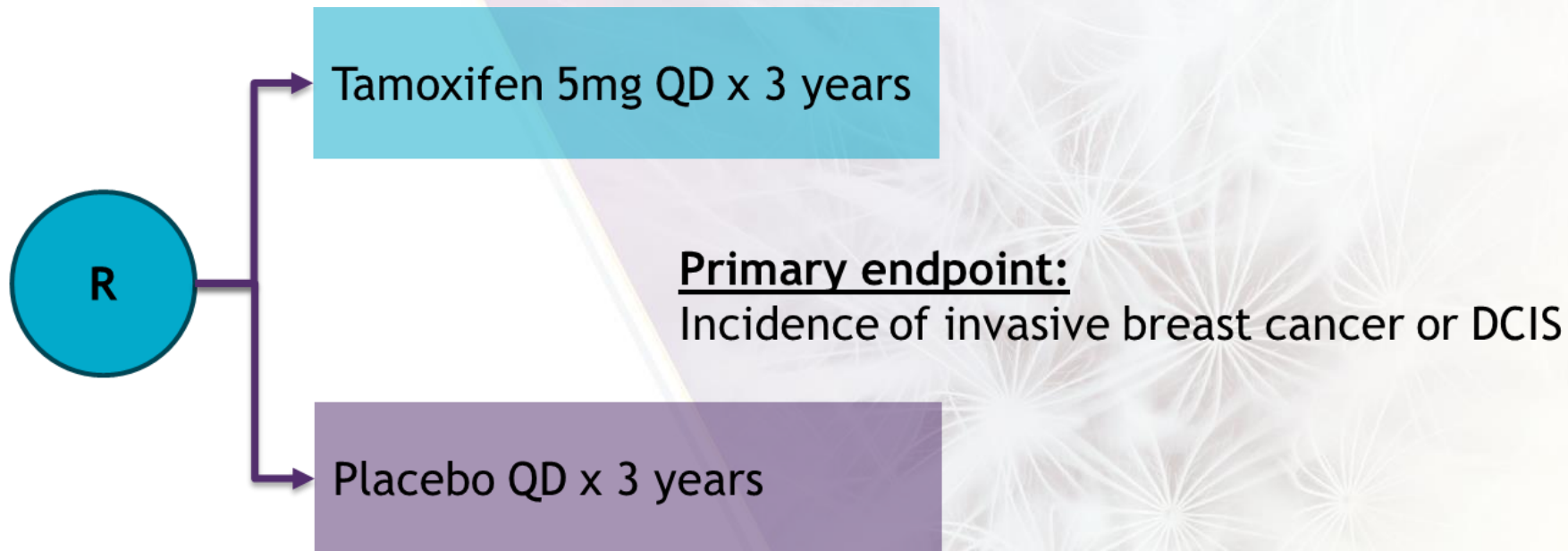*Monarch-E Trial: iDFS according to relative dose intensity (RDI)**
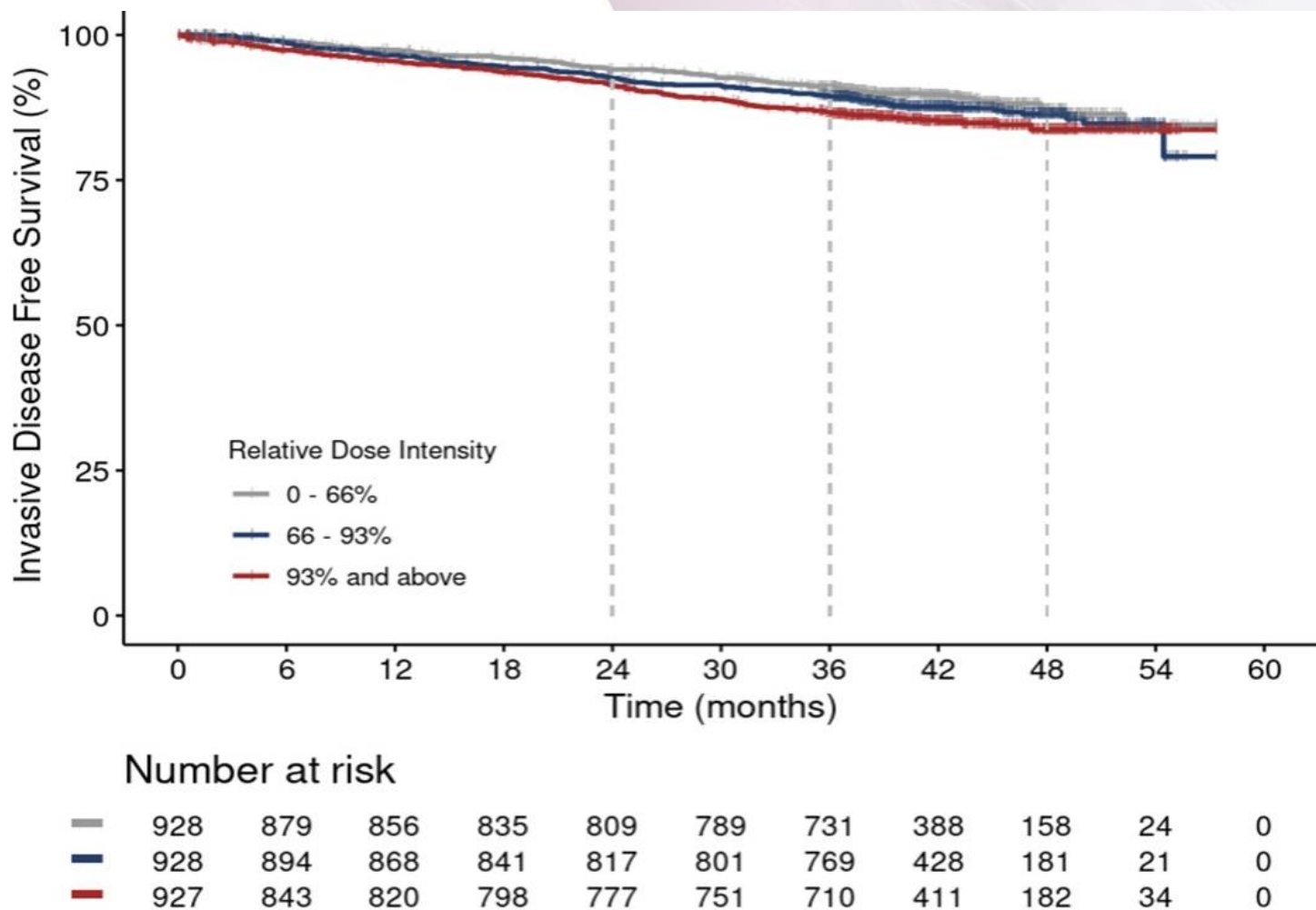
*RDI is defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose (150mg BID)

Hamilton E et al. ASCO 2023

Adjuvant CDK4/6 inhibitors

AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IA	T1N0		
Stage IB	T0N1mi		
	T1N1mi		G3 or Ki67 $\geq$ 20%
Stage IIA	T0N1		
	T1N1		G3 or Ki67 $\geq$ 20%
	T2N0	G3, or G2 with Ki-67 $\geq$ 20% or high genomic risk[c]	
Stage IIB	T2N1		G3 or Ki67 $\geq$ 20%
	T3N0		
Stage IIIA	T0N2		
	T1N2		
	T2N2		
	T3N1		
	T3N2		
Stage IIIB	T4N0		
	T4N1		
	T4N2		
Stage IIIC	Any TN3		

- Pre- and postmenopausal women
- Men

Choice of therapy will depend on approval, access, risk, long-term efficacy, safety profile, and patient preference

Not to forget: **gBRCA testing** in patients eligible for olaparib (OlympiA)

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement;; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm bu less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing breast cancer. [a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3). [b] Capped at 40% ($\approx$ 2000 patients). Simplified inclusion criteria are used in the illustration. [c] High risk as determined by Oncotype DX, clin Risk Score.
References: 1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(suppl 15) [abs E011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020; [5]https://clinicaltrials.gov/ct2/show/NCT03155997

Harbeck N, ASCO 2023

Luminal Breast Cancer: De-escalating adjuvant treatment

TAM-01: Low-dose tamoxifen for secondary prevention

Women ≤75 years
ECOG 0-1
ER/PgR+ or unk
Operated ADH, DCIS, or LCIS*

R

Tamoxifen 5mg QD x 3 years

Placebo QD x 3 years

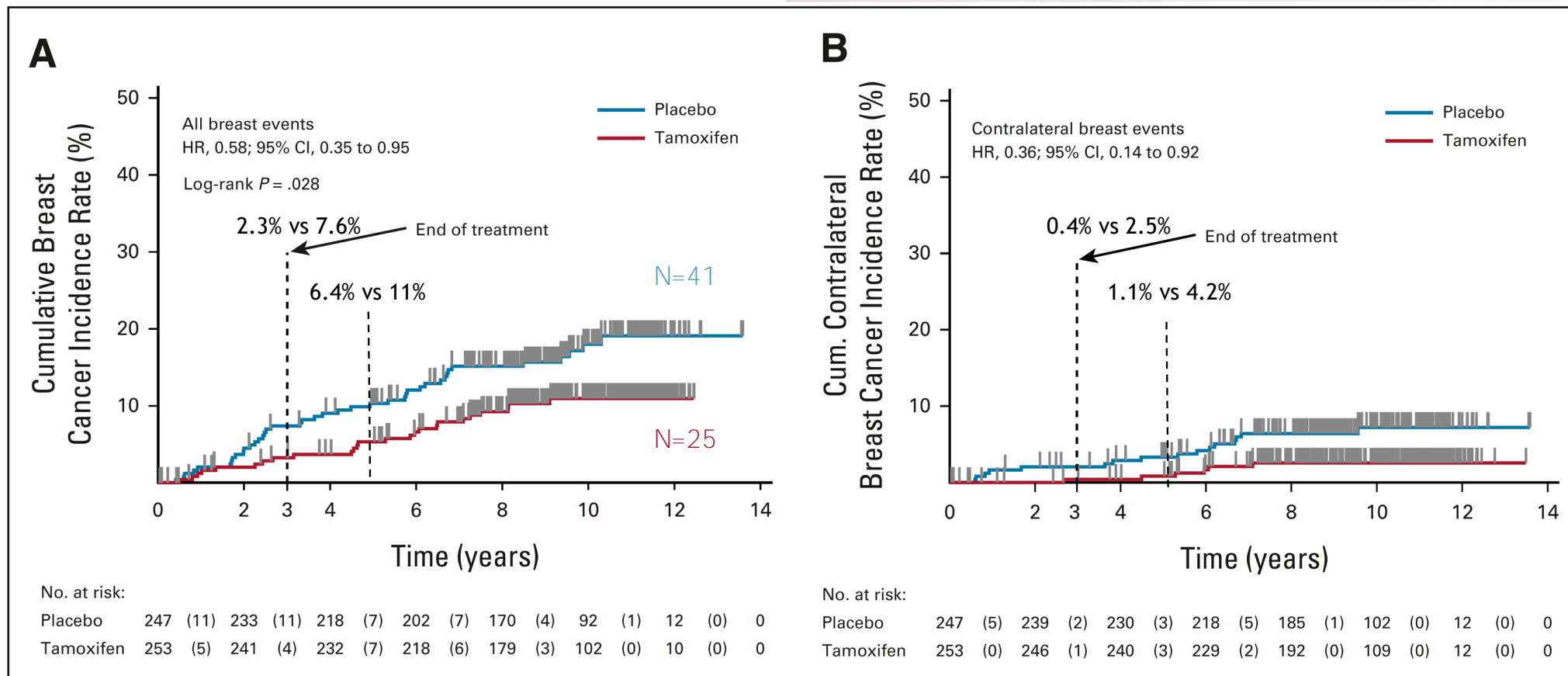**Primary endpoint:**
Incidence of invasive breast cancer or DCIS

- Mean age 54
- Pre-menopausal ~40%
- ADH 20%, LCIS 10%, DCIS 70%
- Received RT 61%

*ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ

De Censi A et al, SABCS 2022; Lazzeroni M et al. J Clin Oncol E-pub March 2023

Luminal Breast Cancer: De-escalating adjuvant treatment

TAM-01: Low-dose tamoxifen for secondary prevention

A

All breast events
HR, 0.58; 95% CI, 0.35 to 0.95

Log-rank *P* = .028

2.3% vs 7.6% — End of treatment

6.4% vs 11%

N=41

N=25

— Placebo
— Tamoxifen

Cumulative Breast Cancer Incidence Rate (%)

Time (years)

No. at risk:

Placebo	247	(11)	233	(11)	218	(7)	202	(7)	170	(4)	92	(1)	12	(0)	0
Tamoxifen	253	(5)	241	(4)	232	(7)	218	(6)	179	(3)	102	(0)	10	(0)	0

B

Contralateral breast events
HR, 0.36; 95% CI, 0.14 to 0.92

0.4% vs 2.5% — End of treatment

1.1% vs 4.2%

— Placebo
— Tamoxifen

Cum. Contralateral Breast Cancer Incidence Rate (%)

Time (years)

No. at risk:

Placebo	247	(5)	239	(2)	230	(3)	218	(5)	185	(1)	102	(0)	12	(0)	0
Tamoxifen	253	(0)	246	(1)	240	(3)	229	(2)	192	(0)	109	(0)	12	(0)	0

Tamoxifen 5 mg once daily for 3 years significantly prevents recurrence from noninvasive breast cancer after 7 years from treatment cessation without long-term adverse events

De Censi A et al, SABCS 2022; Lazzeroni M et al. J Clin Oncol E-pub March 2023

Luminal Breast Cancer: De-escalating adjuvant treatment

POSITIVE Trial: Is it safe to temporarily interrupt ET to attempt pregnancy?

N=518, median follow-up 41 months

- Pre-menopausal women wishing to become pregnant
- Age ≤42
- History of stage I-III HR+ BC
- 18-30 months of prior adjuvant ET
- No clinical evidence of recurrence

Partridge AH et al. SABCS 2022; Partridge AH et al. N Engl J Med 2023;388:1645-56

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ENROLLMENT
(within 1 month of stopping ET)

Stop ET

Resume ET
to complete
5(-10) years

| 18-30 months adjuvant ET | 3 months wash out | Up to 2 years' break to allow conception, delivery ± breast feeding | Follow up |

0   3   6   12   24 mos   10 yrs
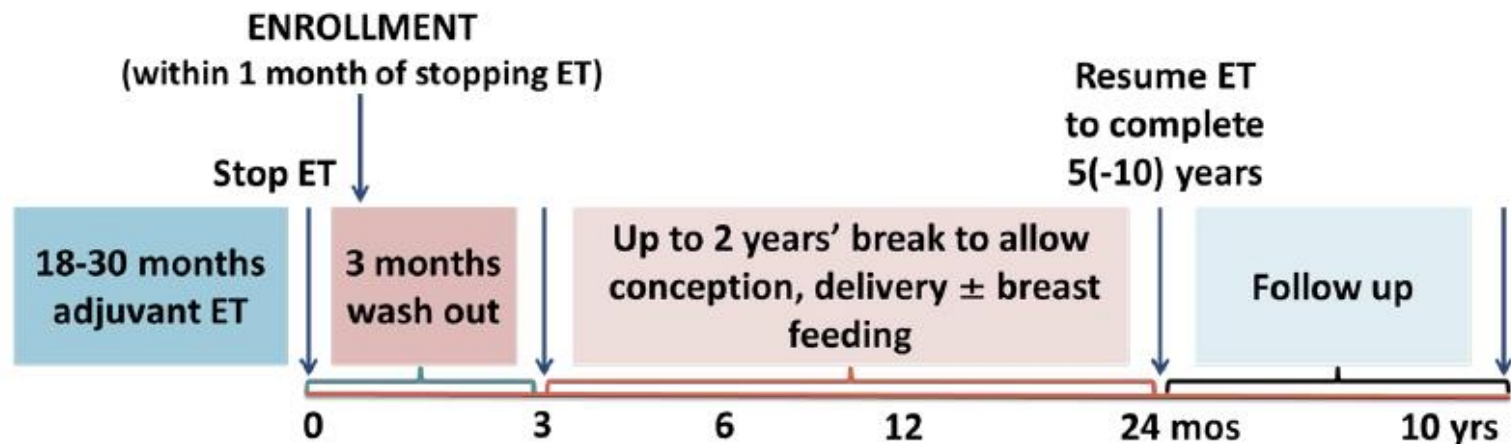
Patients' characteristics
- Median age 37; 75% with no prior births
- Stage I 47%, stage II 47%, stage III 6%
- Median duration of ET prior to enrollment: 23.4 months
    - SERM alone 42%
    - SERM + OFS 36%
    - AI + OFS 16%
- Prior (neo)adjuvant CT 62%

Partridge AH et al. SABCS 2022; Partridge AH et al. N Engl J Med 2023;388:1645-56

Luminal Breast Cancer: De-escalating adjuvant treatment

POSITIVE Trial: Is it safe to temporarily interrupt ET to attempt pregnancy? YES!

All population
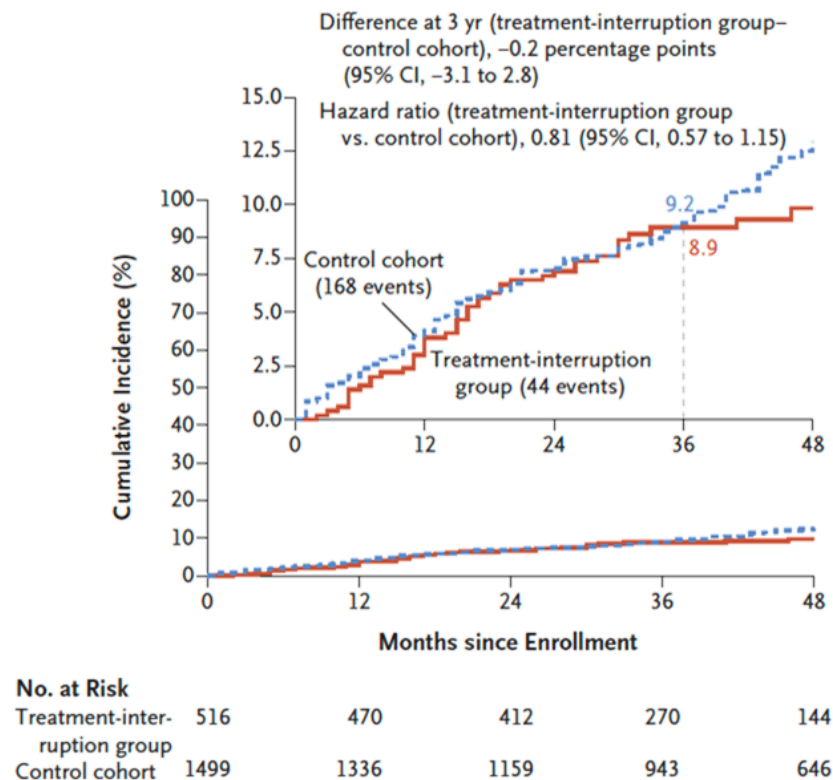
Pregnant vs non-pregnant participants
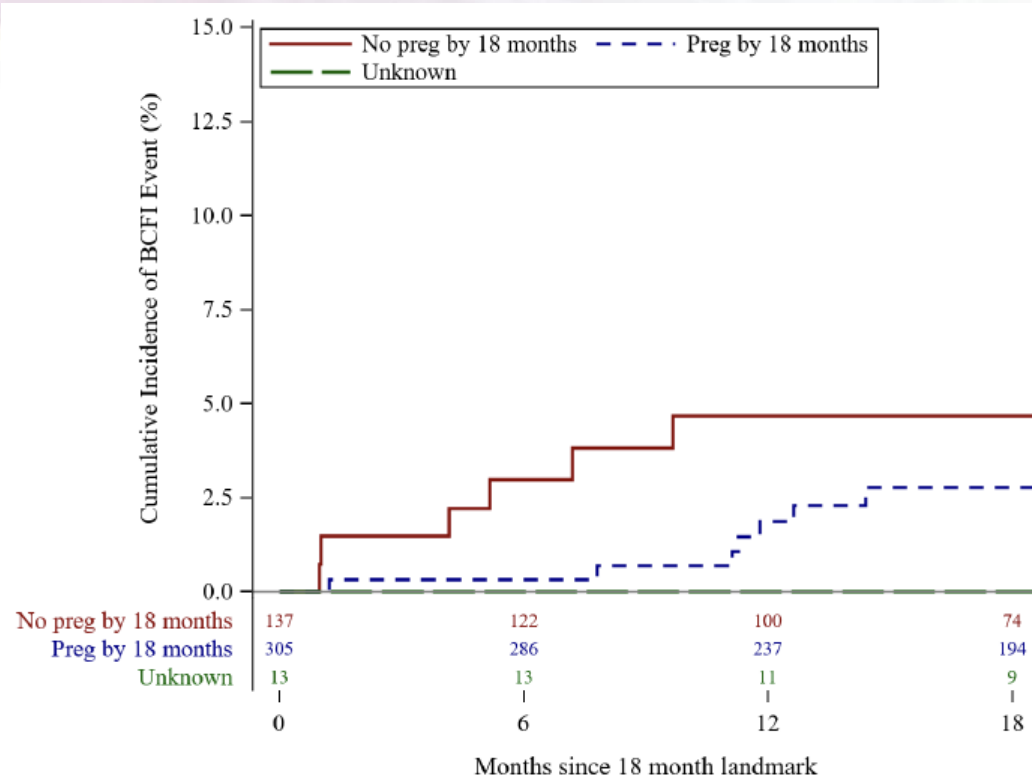
No impact in short-term disease outcomes
- 3y BCFI similar to SOFT / TEXT (and varied according to clinical-pathological characteristics
- BCFI events not different between pregnant and non pregnant participants

Birth defects were low (2%), not clearly associated with treatment exposure

Partridge AH et al. SABCS 2022; Partridge AH et al. N Engl J Med 2023;388:1645-56

HER2+ breast cancer: De-escalating therapy using biomarkers

Pérez-García J et al. Lancet Oncol. 2021 Jun;22(6):858-871 and Cortés J et al. ASCO 2023

HER2+ breast cancer: De-escalating therapy using biomarkers

PHERGAIN Trial: using PET-CT to tailor therapy

Pérez-García J et al. Lancet Oncol. 2021 Jun;22(6):858-871 and Cortés J et al. ASCO 2023

HER2+ breast cancer: De-escalating therapy using biomarkers

PHERGAIN Trial: using PET-CT to tailor therapy

- Excellent pCR (with and without CT) in patients with PET response
- Patients with no PET response have low pCR rates, independently of the use of CT

Pérez-García J et al. Lancet Oncol. 2021 Jun;22(6):858-871

HER2+ breast cancer: De-escalating therapy using biomarkers

PHERGAIN Trial: using PET-CT to tailor therapy

Cortés J et al. ASCO 2023
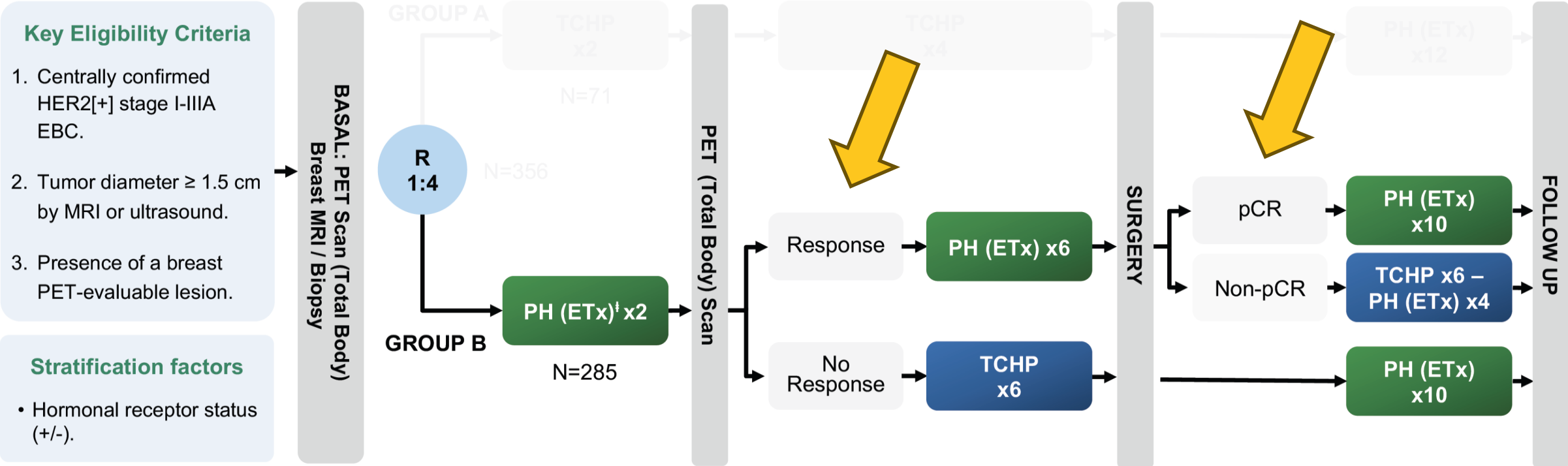
HER2+ breast cancer: De-escalating therapy using biomarkers

PHERGAIN Trial: using PET-CT to tailor therapy

In patients with PET response after 2 cycles of HP (**Group B**), outcomes are excellent, independently of the use of neoadjuvant CT
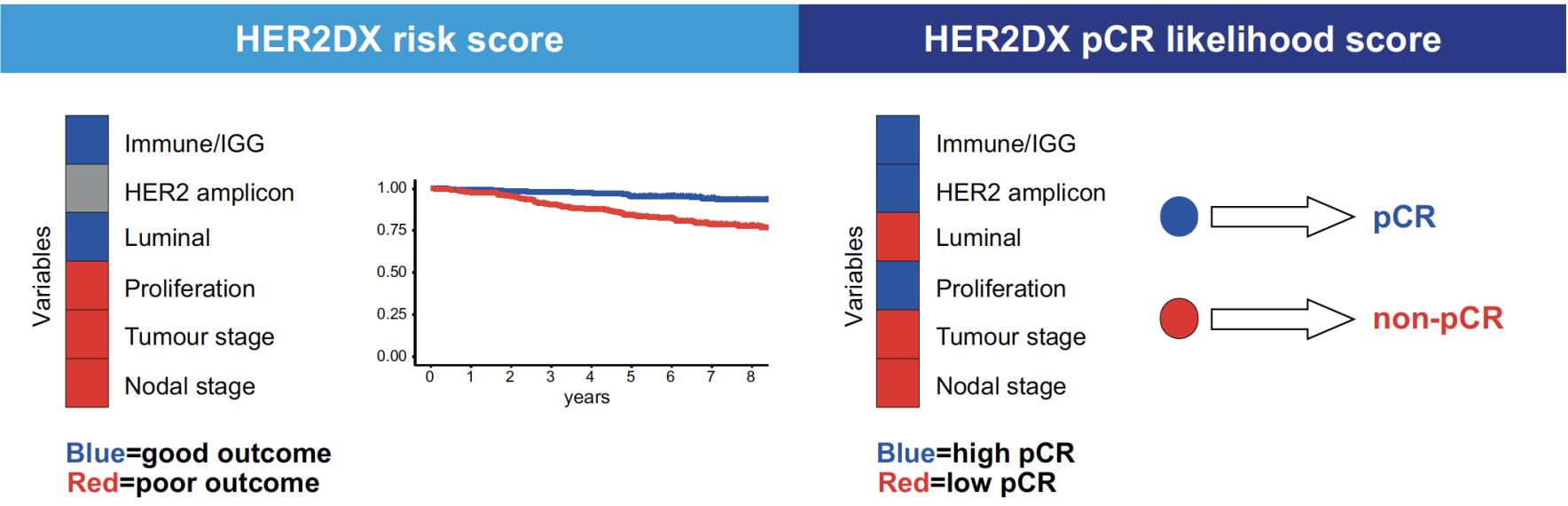
	Group A (n = 63)	Group B (n = 267)	Group B without CT (n = 86)
3-year iDFS	98.3%	95.4%	98.8%
(95% CI)	(95.1–100%)	(92.8–98.0%)	(96.3–100%)
3-year DDFS	98.3%	96.5%	100%
(95% CI)	(95.1–100%)	(94.3–98.8%)	(100–100%)
	(n = 71)	(n = 285)	(n = 86)
3-year EFS	98.4%	93.5%	98.8%
(95% CI)	(95.3–100%)	(90.7–96.5%)	(96.6–100%)
3-year OS	98.4%	98.5%	100%
(95% CI)	(95.3–100%)	(97.1–100%)	(100–100%)

None of these comparisons between the groups reached statistical significance.
iDFS and DDFS are defined from the time of surgery; EFS and OS are defined from randomization.

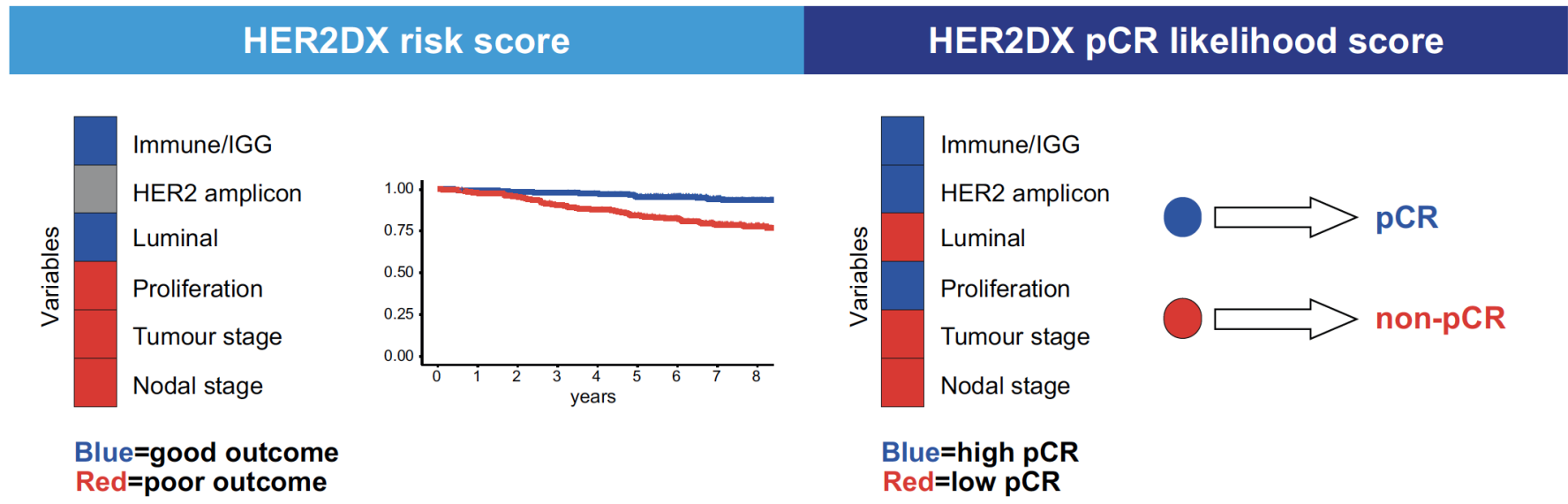12 iDFS events: 11 relapse (8 distant), 1 non-related death witout recurrence

Cortés J et al. ASCO 2023

HER2+ breast cancer: De-escalating therapy using biomarkers
HER2DX

HER2DX risk score	HER2DX pCR likelihood score

HER2DX risk score

Variables:
- Immune/IGG
- HER2 amplicon
- Luminal
- Proliferation
- Tumour stage
- Nodal stage

Blue=good outcome
Red=poor outcome

HER2DX pCR likelihood score

Variables:
- Immune/IGG
- HER2 amplicon
- Luminal
- Proliferation
- Tumour stage
- Nodal stage

→ pCR
→ non-pCR

Blue=high pCR
Red=low pCR

Prat A et al. EBioMedicine. 2022 Jan;75:103801 | Villacampa G et al. Ann Oncol. 2023 Jun 9:S0923-7534(23)00721-4

HER2+ breast cancer: De-escalating therapy using biomarkers
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- HER2 amplicon
- Luminal
- Proliferation
- Tumour stage
- Nodal stage

pCR

non-pCR

Blue=high pCR
Red=low pCR

- HER2DX **pCR score** predicts pCR independently of HR status and treatment regimen
  - **pCR-high** group benefits the most from neoadjuvant dual HER2 blockade
  - **pCR-medium** group benefits the most from multi-agent CT vs single taxane
  - **pCR-low** group shows pCR rates <30% across all therapies
- HER2DX **low-risk** is significantly associated with risk of relapse independently of pCR status
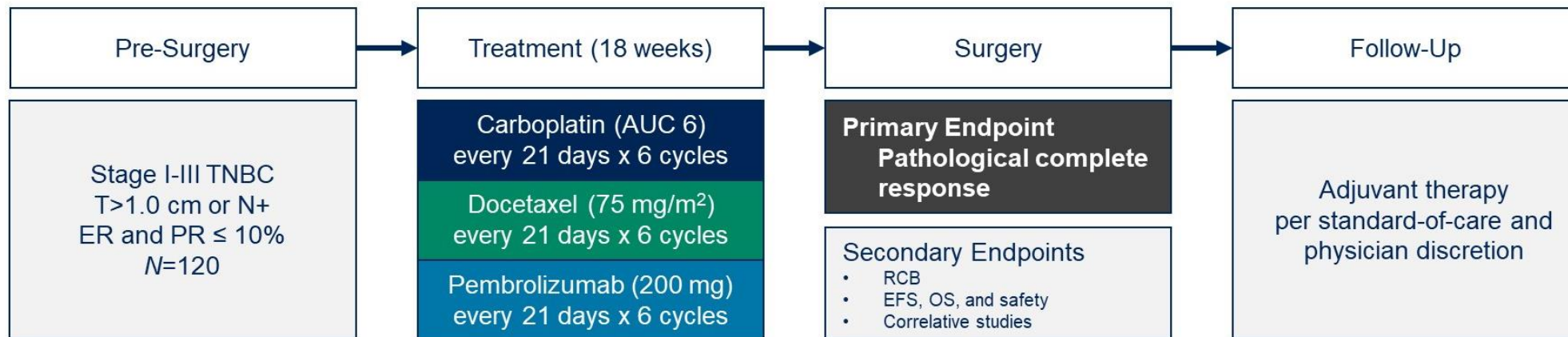- **HER2DX high-risk and pCR-low group of patients is an unmet need population**

Prat A et al. EBioMedicine. 2022 Jan;75:103801 | Villacampa G et al. Ann Oncol. 2023 Jun 9:S0923-7534(23)00721-4

Triple Negative Breast Cancer: de-escalating treatment

Neo-PACT: Anthracycline-free regimen for early TNBC
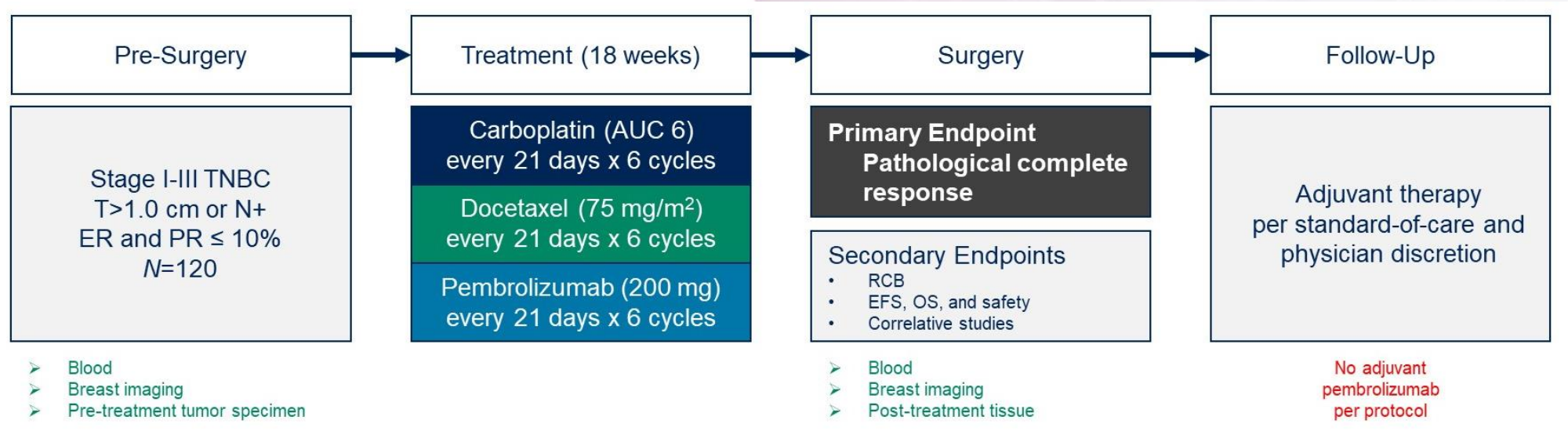
Pre-Surgery	Treatment (18 weeks)	Surgery	Follow-Up
Stage I-III TNBC T>1.0 cm or N+ ER and PR ≤ 10% N=120	Carboplatin (AUC 6) every 21 days x 6 cycles Docetaxel (75 mg/m²) every 21 days x 6 cycles Pembrolizumab (200 mg) every 21 days x 6 cycles	**Primary Endpoint Pathological complete response** Secondary Endpoints • RCB • EFS, OS, and safety • Correlative studies	Adjuvant therapy per standard-of-care and physician discretion
➤ Blood ➤ Breast imaging ➤ Pre-treatment tumor specimen		➤ Blood ➤ Breast imaging ➤ Post-treatment tissue	No adjuvant pembrolizumab per protocol

Sharma P et al. ASCO 2022 | Stecklein SR et al. ASCO 2023

Triple Negative Breast Cancer: de-escalating treatment

Neo-PACT: Anthracycline-free regimen for early TNBC

Pre-Surgery → Treatment (18 weeks) → Surgery → Follow-Up

Pre-Surgery
Stage I-III TNBC
T>1.0 cm or N+
ER and PR ≤ 10%
N=120

➢ Blood
➢ Breast imaging
➢ Pre-treatment tumor specimen

Treatment (18 weeks)
Carboplatin (AUC 6)
every 21 days x 6 cycles

Docetaxel (75 mg/m²)
every 21 days x 6 cycles

Pembrolizumab (200 mg)
every 21 days x 6 cycles

Surgery
Primary Endpoint
Pathological complete response

Secondary Endpoints
• RCB
• EFS, OS, and safety
• Correlative studies

➢ Blood
➢ Breast imaging
➢ Post-treatment tissue

Follow-Up
Adjuvant therapy per standard-of-care and physician discretion

No adjuvant pembrolizumab per protocol

pCR defined as no invasive tumor in breast and axilla

Pathologic Complete Response (%)
All 58%
Nodal Status: Pos 65%, Neg 45%
ER/PR Expression: < 1% 58%, 1-10% 56%
sTILs: ≥ 20% 73%, < 20% 41%

2-year EFS
Median follow-up 24.4 months

pCR 98%
ALL 89%
Residual disease 78%

Residual disease vs pCR:
HR 9.12 (95% CI 1.98-41.94),
log-rank p=0.001

Event-Free Survival (%)
Months since diagnosis

	Number at risk						
All	113	108	95	75	54	37	18
pCR	63	62	55	48	38	28	13
Residual disease	49	46	40	27	16	9	5

Survival analysis includes all patients in the ITT population except for N=2 who are awaiting surgery

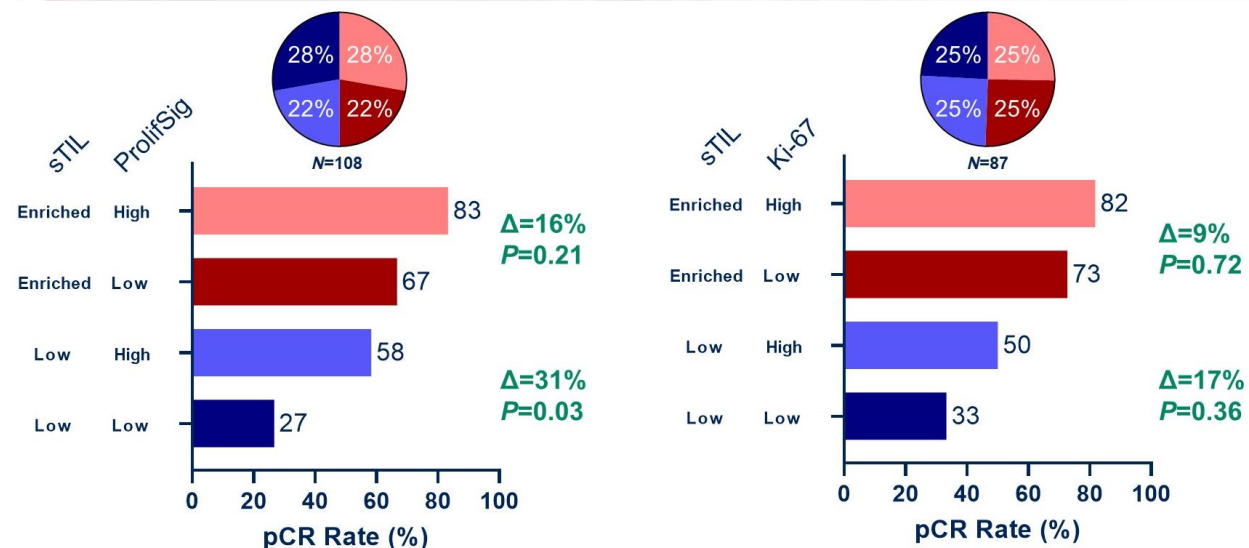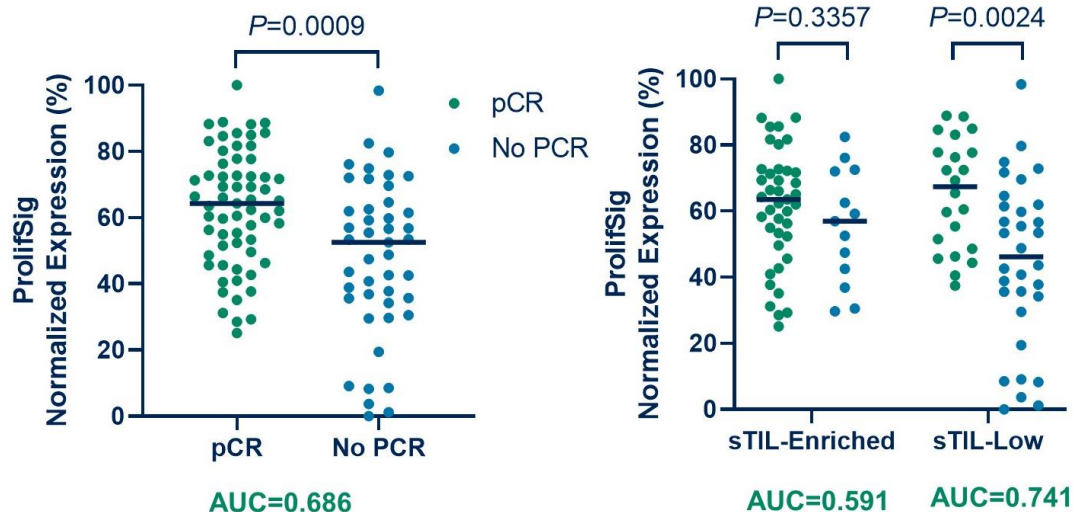Sharma P et al. ASCO 2022 | Stecklein SR et al. ASCO 2023

Triple Negative Breast Cancer: de-escalating treatment

Neo-PACT: refining pCR prediction

ProlifSig is associated with pCR in sTIL-Low (but not in sTIL-enriched) TNBC
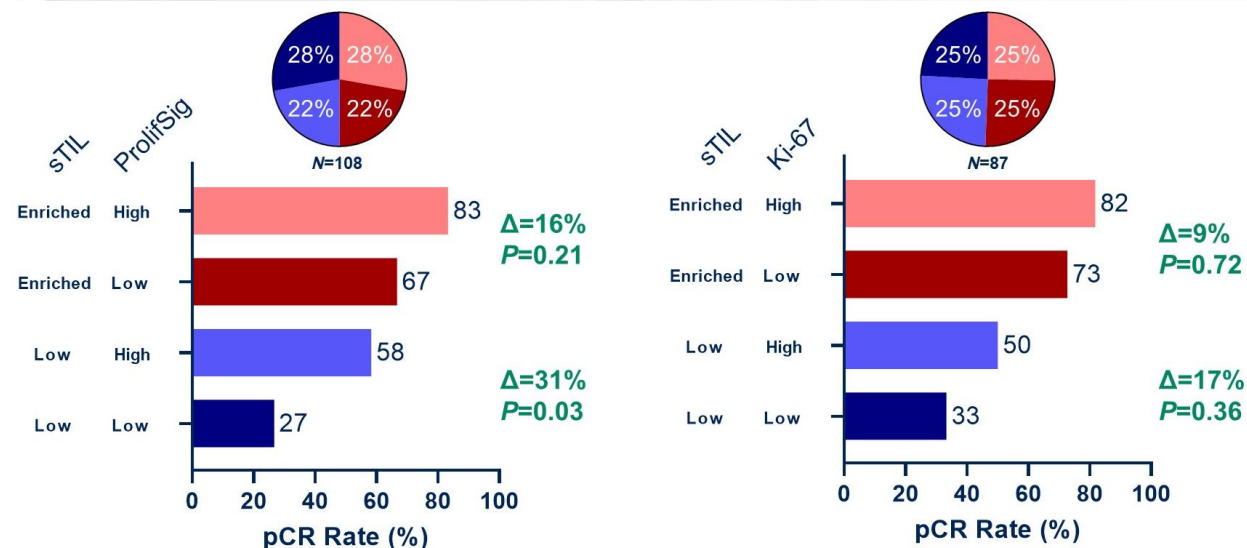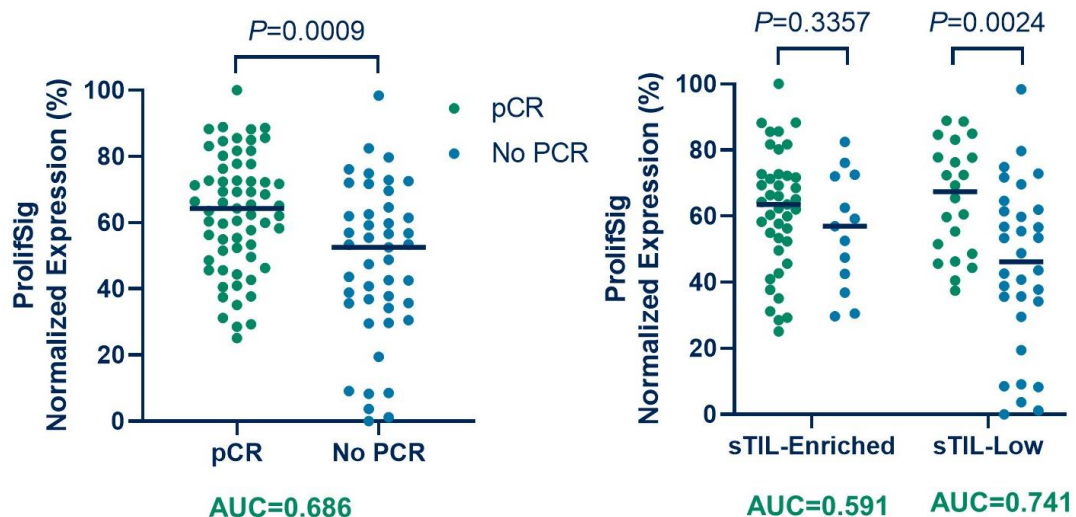
pCR rate by sTIL and ProlifSig class

sTIL-Enriched = ≥ 20%; sTIL-Low = < 20%; ProlifSig-High= ≥ median; ProlifSig-Low = < median; Ki-67-High = ≥ median; Ki-67-Low = < median

Stecklein SR et al. ASCO 2023

Triple Negative Breast Cancer: de-escalating treatment

Neo-PACT: refining pCR prediction

ProlifSig is associated with pCR in sTIL-Low (but not in sTIL-enriched) TNBC

pCR rate by sTIL and ProlifSig class

AUC=0.686

AUC=0.591 AUC=0.741

sTIL-Enriched = ≥ 20%; sTIL-Low = < 20%; ProlifSig-High= ≥ median; ProlifSig-Low = < median; Ki-67-High = ≥ median; Ki-67-Low = < median

Multivariate analysis

Variable	OR	95% CI	P
sTILs (Continuous)	1.03	1.01-1.04	0.001
ProlifSig (Continuous)	3.30	1.46-7.46	0.004
T Category (T1-2 vs. T3-4)	0.79	0.24-2.60	0.701
N Status (Neg. vs. Pos.)	2.93	1.15-7.49	0.025

Stecklein SR et al. ASCO 2023
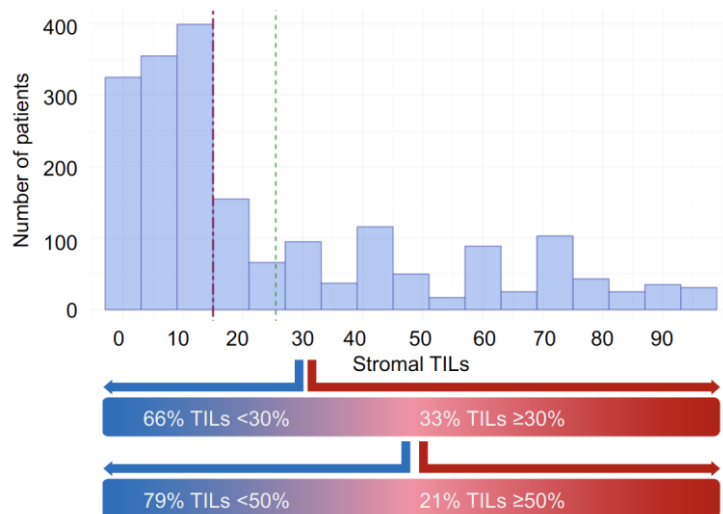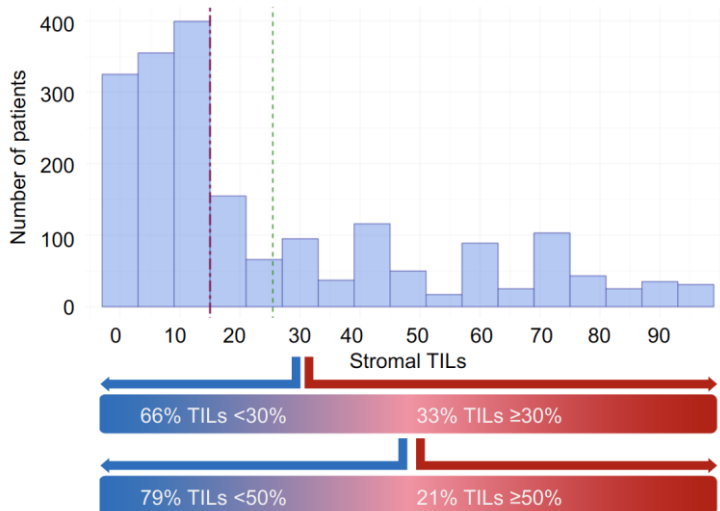
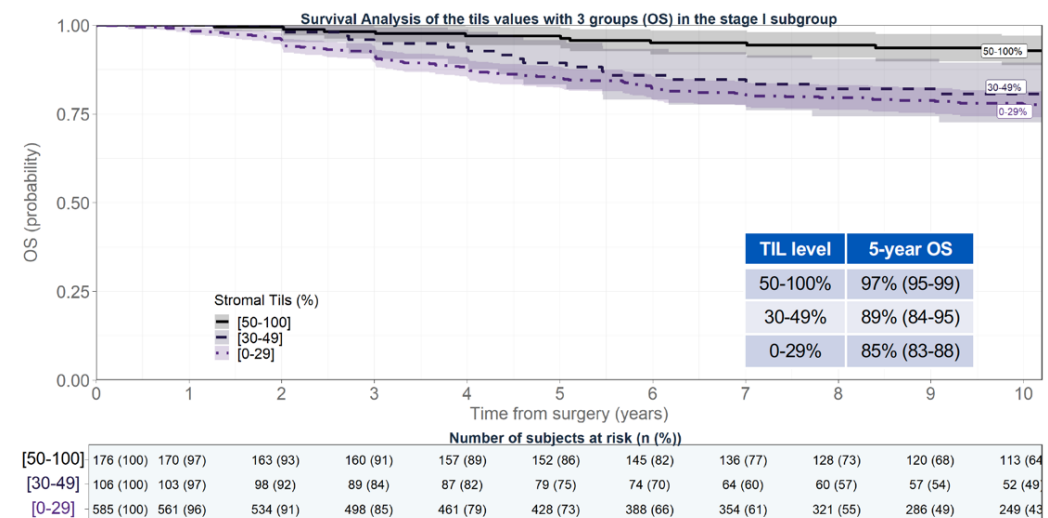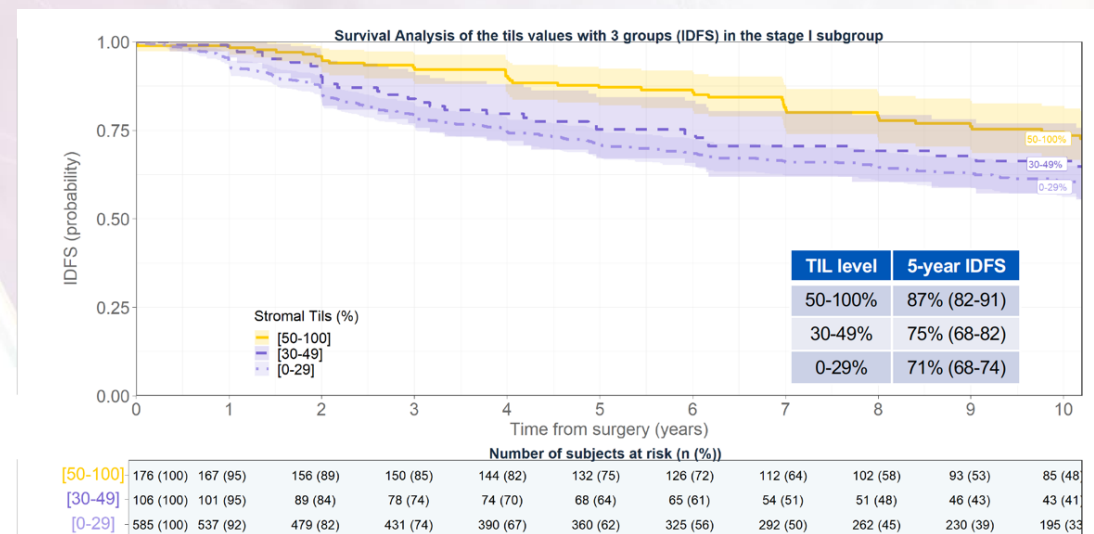# Triple Negative Breast Cancer: de-escalating treatment

Prognostic of TILs in early TNBC

Individual patient data pooled analysis of 13 international
cohorts of patients with TNBC treated with locoregional
therapy but no systemic therapy
N=1966, median follow-up 30.4 years; most N0 (86.6%),
median % of stromal TILs 15%

Proportion of TILs

Léon-Ferré R et al. SABCS 2022

Triple Negative Breast Cancer: de-escalating treatment

Prognostic of TILs in early TNBC

Stage I

Individual patient data pooled analysis of 13 international cohorts of patients with TNBC treated with locoregional therapy but no systemic therapy
N=1966, median follow-up 30.4 years; most N0 (86.6%), median % of stromal TILs 15%
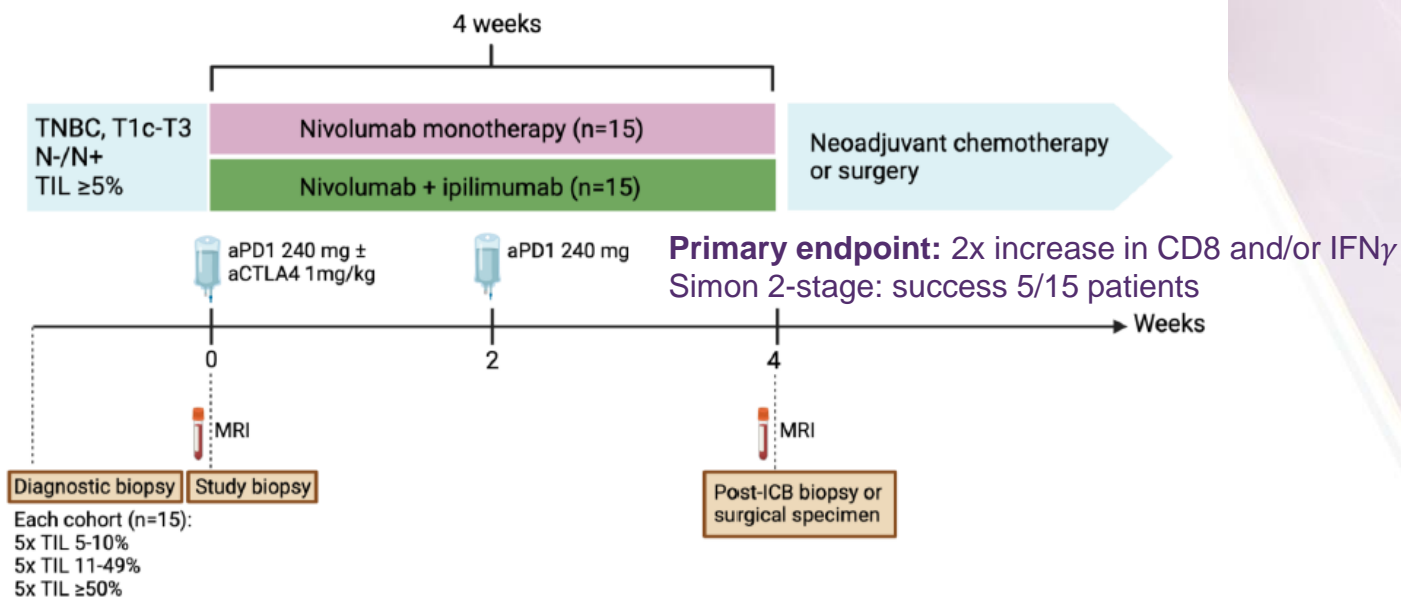
Proportion of TILs

Number of patients (y-axis), **Stromal TILs** (x-axis: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90)

66% TILs <30% | 33% TILs ≥30%

79% TILs <50% | 21% TILs ≥50%

Survival Analysis of the tils values with 3 groups (IDFS) in the stage I subgroup

Stromal Tils (%)
— [50-100]
- - [30-49]
···· [0-29]

TIL level	5-year IDFS
50-100%	87% (82-91)
30-49%	75% (68-82)
0-29%	71% (68-74)

Number of subjects at risk (n (%))

[50-100]	176 (100)	167 (95)	156 (89)	150 (85)	144 (82)	132 (75)	126 (72)	112 (64)	102 (58)	93 (53)	85 (48)
[30-49]	106 (100)	101 (95)	89 (84)	78 (74)	74 (70)	68 (64)	65 (61)	54 (51)	51 (48)	46 (43)	43 (41)
[0-29]	585 (100)	537 (92)	479 (82)	431 (74)	390 (67)	360 (62)	325 (56)	292 (50)	262 (45)	230 (39)	195 (33)

Survival Analysis of the tils values with 3 groups (OS) in the stage I subgroup

Stromal Tils (%)
— [50-100]
- - [30-49]
···· [0-29]

TIL level	5-year OS
50-100%	97% (95-99)
30-49%	89% (84-95)
0-29%	85% (83-88)

Number of subjects at risk (n (%))

[50-100]	176 (100)	170 (97)	163 (93)	160 (91)	157 (89)	152 (86)	145 (82)	136 (77)	128 (73)	120 (68)	113 (64)
[30-49]	106 (100)	103 (97)	98 (92)	89 (84)	87 (82)	79 (75)	74 (70)	64 (60)	60 (57)	57 (54)	52 (49)
[0-29]	585 (100)	561 (96)	534 (91)	498 (85)	461 (79)	428 (73)	388 (66)	354 (61)	321 (55)	286 (49)	249 (43)

Léon-Ferré R et al. SABCS 2022

Triple Negative Breast Cancer: de-escalating treatment

BELLINI: targeting immunogenic TNBC with ICI

	Nivo (N=16)	Nivo + Ipi (N=15)
Median age	48 (27-71)	50 (34-67)
Grade 3	93.8%	73.3%
T1	31.3%	40%
N1-3	18.8%	66.7%
gBRCA1/2 mut	18.8%	20%
Median TILs (range)	29 (5-88)	35 (5-90)
PD-L1 CPS (22C3)		
0-1	12.5%	6.7%
2-9	25%	13.3%
≥10	62.5%	73.3%

Kok M et al. ESMO 2022

Triple Negative Breast Cancer: de-escalating treatment

BELLINI: targeting immunogenic TNBC with ICI

Primary endpoint: 2x increase in CD8 and/or IFNγ
Simon 2-stage: success 5/15 patients

Each cohort (n=15):
5x TIL 5-10%
5x TIL 11-49%
5x TIL ≥50%

	Nivo (N=16)	Nivo + Ipi (N=15)
Median age	48 (27-71)	50 (34-67)
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PD-L1 CPS (22C3)		
0-1	12.5%	6.7%
2-9	25%	13.3%
≥10	62.5%	73.3%

- 2-fold increase in CD8 (IHC) and/or interferon gamma (IFNγ, gene expression)

Immune activation	Nivo (N=16)	Nivo + Ipi (N=15)
No 2 fold increase	7 (43.8%)	6 (40.0%)
2 fold increase	8 (53.3%)	9 (60.0%)

- Basket expansion to stage II allowed if at least 5/15 (30%) patients show immune activation -> both cohorts meet the criterion

- Poor correlation between 2-fold increase in CD8/IFNγ and MRI
-> Tumors very high in CD8/IFNγ at baseline, less likely to have 2-fold increase

CD8 was assessed using immunohistochemistry and scored using HALO software, corrected for the analysed tissue area (cells /µm2) and supervised by one expert pathologist
IFNγ = single gene expression from bulkRNA sequencing data, similar results obtained with IFNγ-signature based on Ayers et al. J Clin Invest 2017. We included all patients with representative matched samples for CD8 (n=30) and IFNG (n=23).

ORR
3/16 (19%) ■ Nivolumab
4/15 (27%) ■ Nivolumab + Ipilimumab

✳ = Primary resection after ICB
T2N0 > ypT0N0
T2N1 > ypT1bN0
T1cN0 > ypT1aN0

NT = No tumor in +4 weeks biopsy

Of the 7 responders: 3 in TIL high, 4 in TIL intermediate

Kok M et al. ESMO 2022

Summary

What's new in 2023: treatment tailoring and optimization in Early Breast Cancer

Luminal

- CDK4/6i reduce the risk of recurrence in high- and intermediate-risk luminal breast cancer
- NATALEE data, yet very promising, are immature with the current follow-up
- Low-dose tamoxifen is effective for breast cancer prevention with excellent tolerability
- Endocrine therapy may be interrupted to attempt pregnancy without compromising outcomes

Summary

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HER2+

- HER2DX and PET-CT (together with pCR) may be used to tailor treatment of early HER2+ breast cancer

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HER2+

- HER2DX and PET-CT (together with pCR) may be used to tailor treatment of early HER2+ breast cancer

Triple negative

- Anthracyclines-free regimen (docetaxel + carboplatin) with pembrolizumab yields high pCR rates in TNBC
- TILs should be used in prospective clinical trials to de-escalate therapy, at least in stage I TNBC