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# *Early Breast Cancer: systemic therapy*

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MEDICAL EDUCATION

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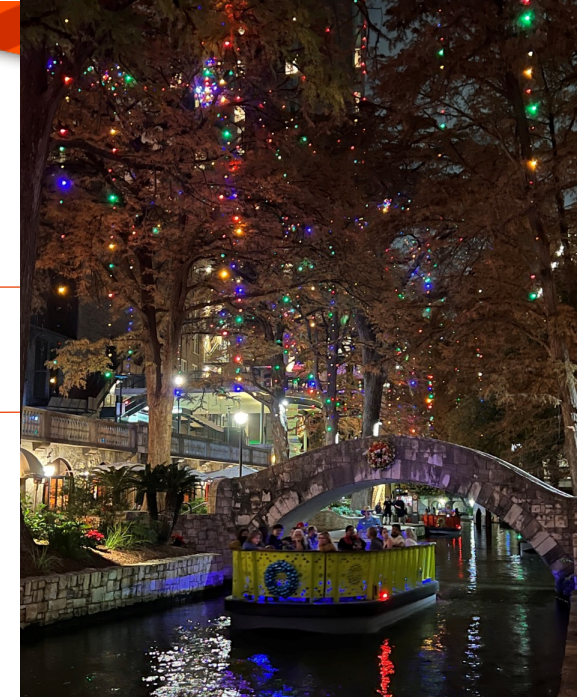
## Financial Disclosure: Hans Wildiers

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- His institution received financial compensation on his behalf for advisory boards, lecture fees and/or consultancy fees from Immutep Pty, MSD, AstraZenca, Daiichi, AbbVie, Lilly, Roche, Eisai, Pfizer, Sirtex, Gilead.
- He received travel support from Pfizer and Roche.

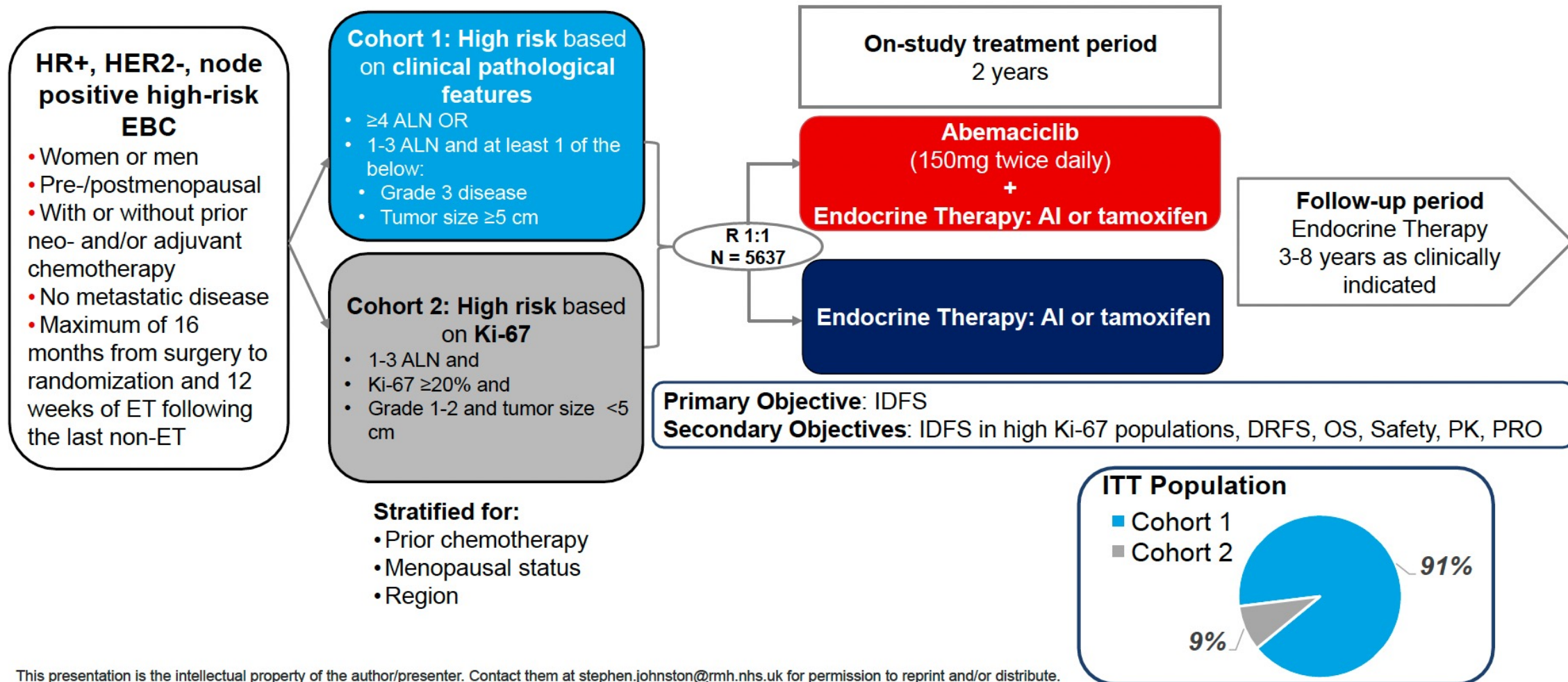
## Overview early breast cancer systemic therapy

- Luminal:
  - Adjuvant abemaciclib
  - Adjuvant everolimus
  - Neo-adj Palbociclib
  - Gene expression profiles
  - HER2 low
- TNBC:
  - Neoadjuvant platinum
  - Neoadjuvant olaparib
- HER2+:
  - APT update (paclitaxel trastuzumab)



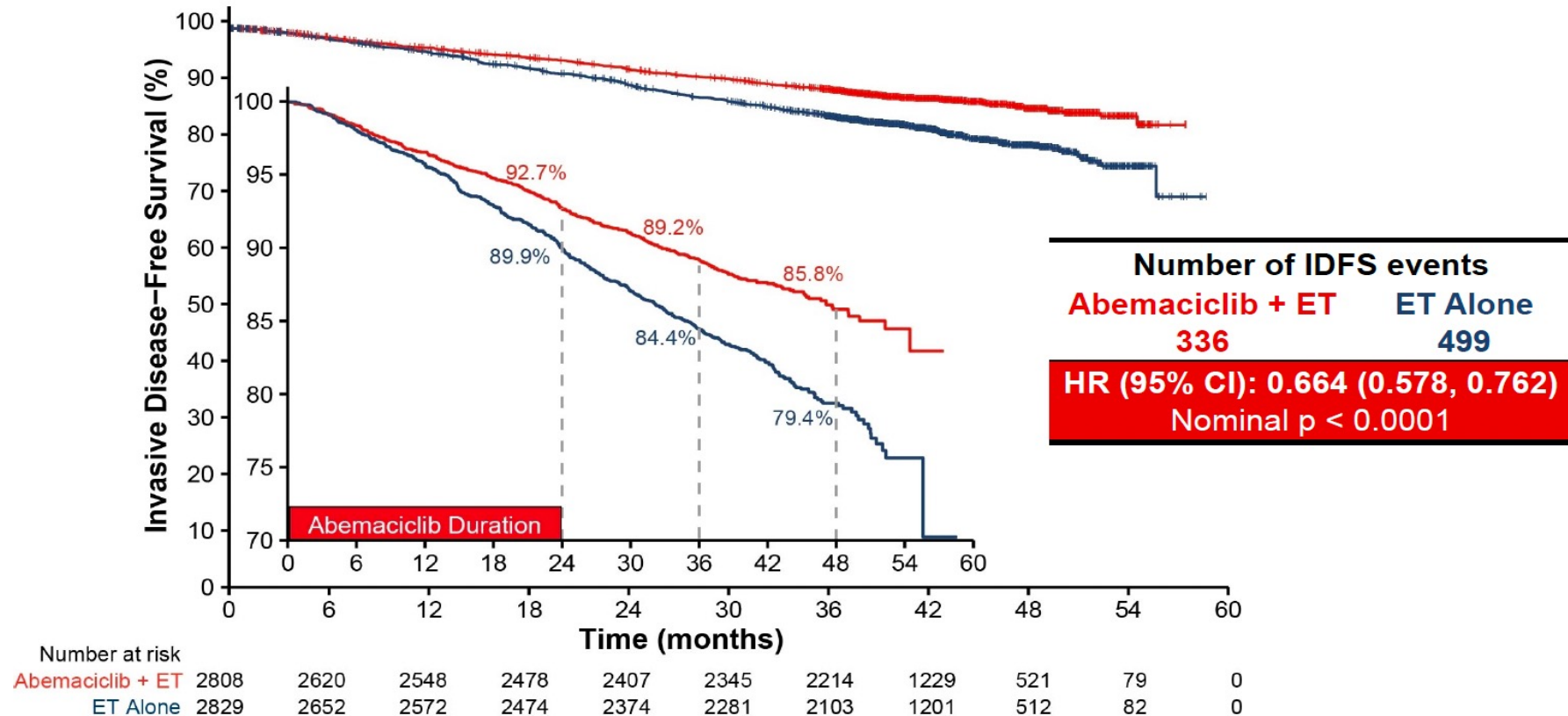


# MonarchE (adjuvant abemaciclib): 4y update



# MonarchE (adjuvant abemaciclib): 4y update

## Invasive Disease Free survival (IDFS)



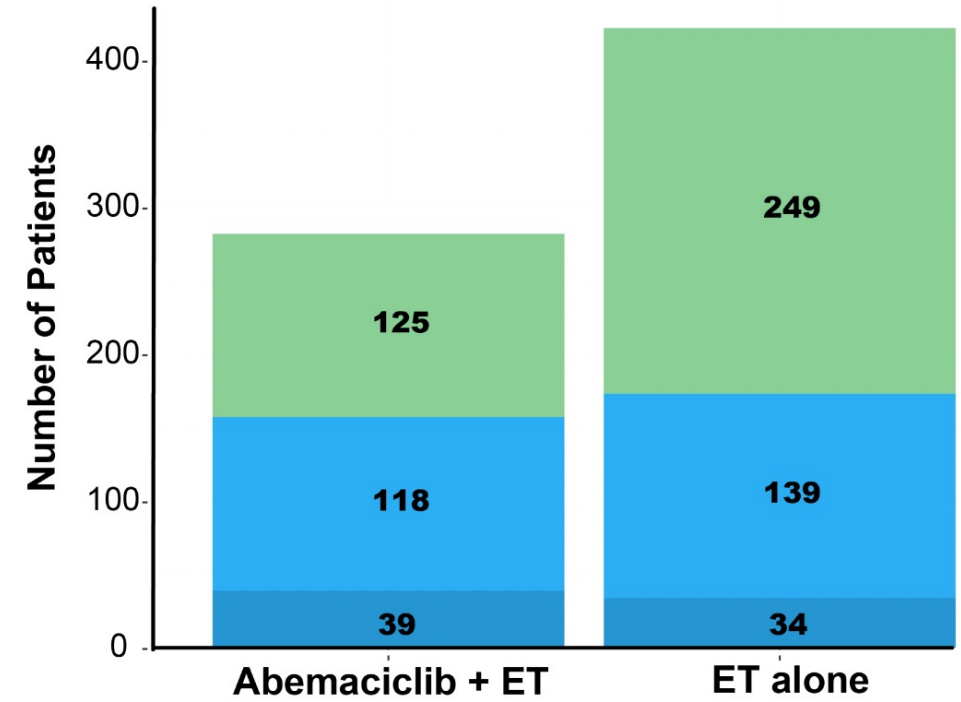
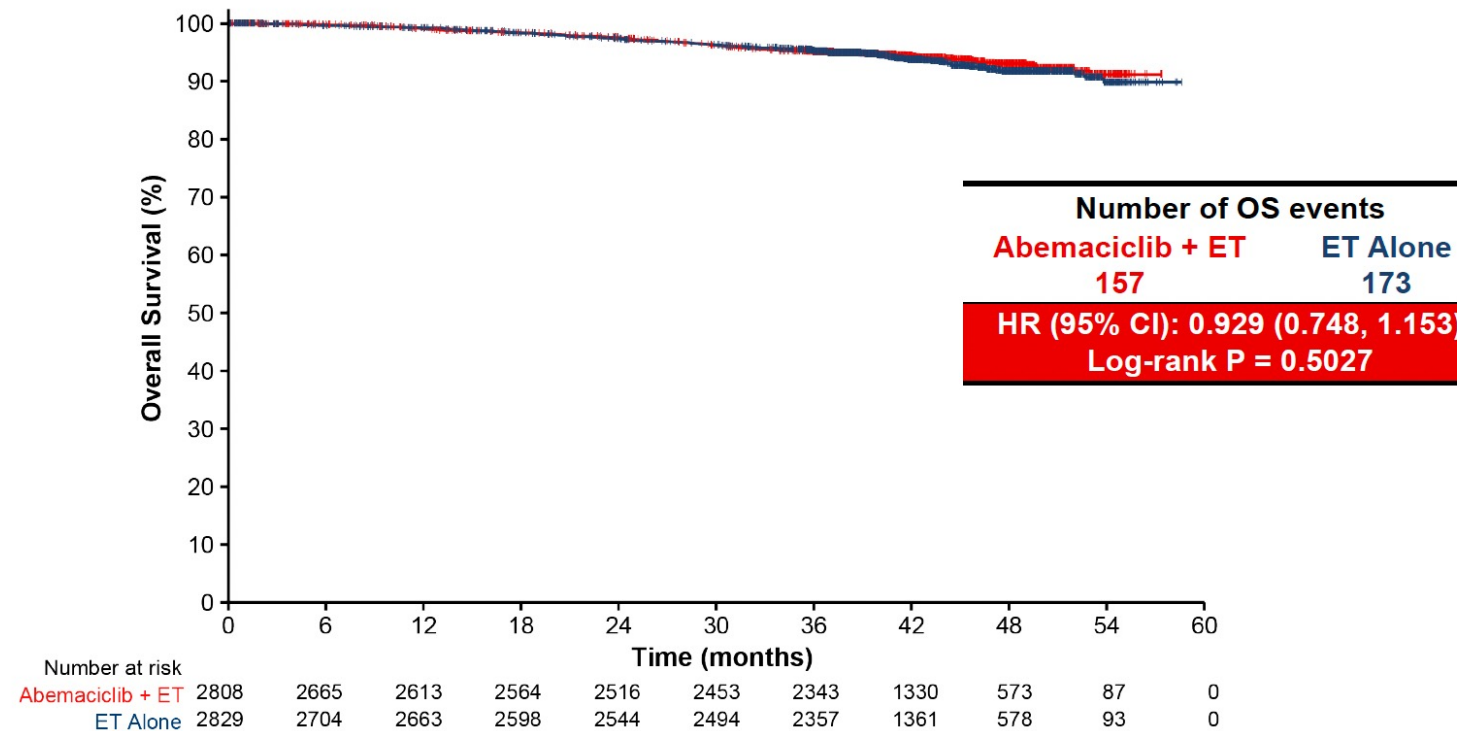
IDFS benefit persists after abemaciclib completion

34% reduction for IDFS events

Absolute difference 2,8%(2y) ; 4,8%(3y) ; **6,4%(4y)**

# MonarchE (adjuvant abemaciclib): 4y update

## Overall Survival (OS)



**Survival Status**

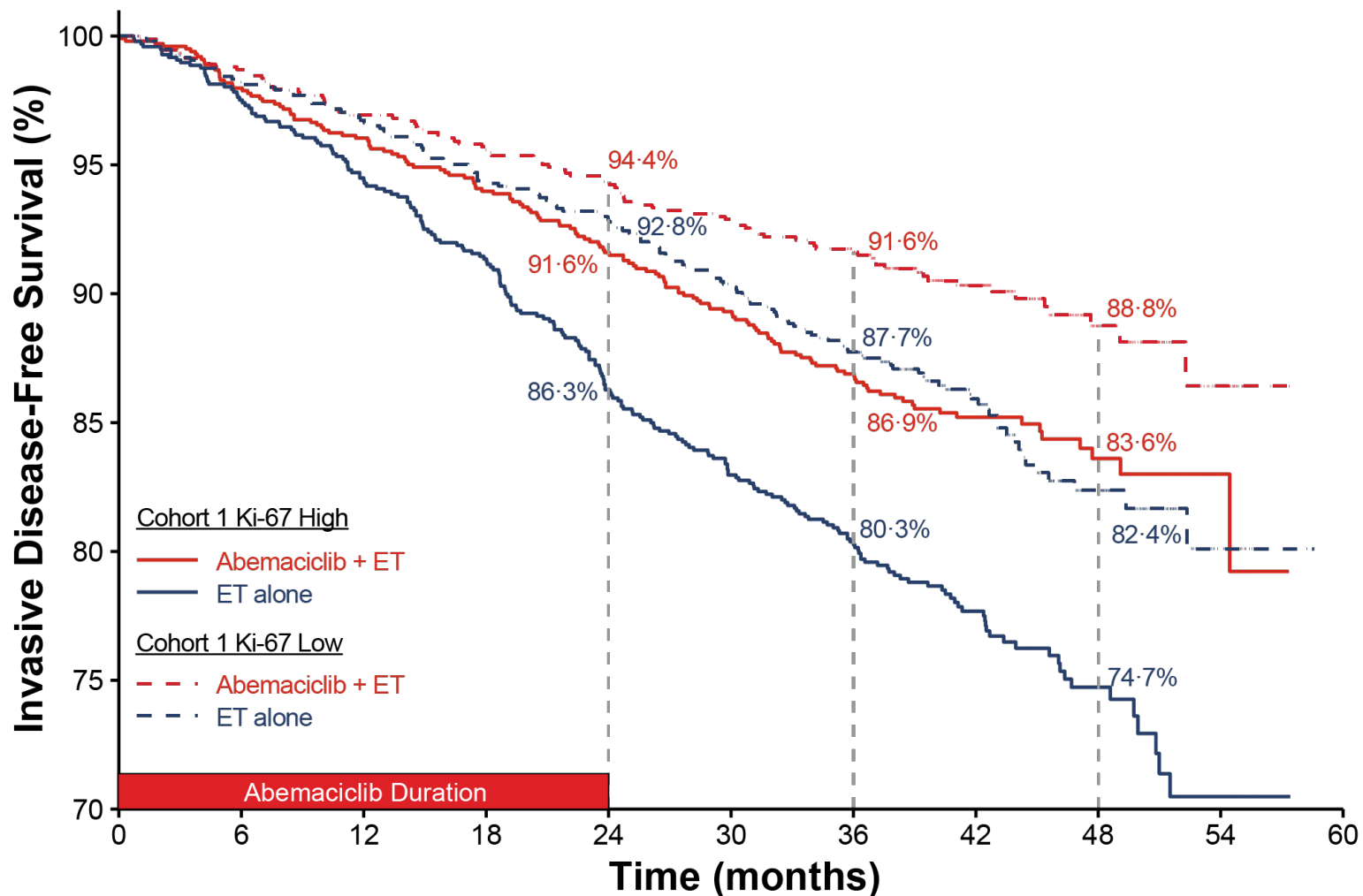
- Alive with metastatic disease
- Deaths due to breast cancer
- Deaths not related to breast cancer

No OS difference at 4y: immature data?

Fewer pts with metastatic disease

# MonarchE (adjuvant abemaciclib): 4y update

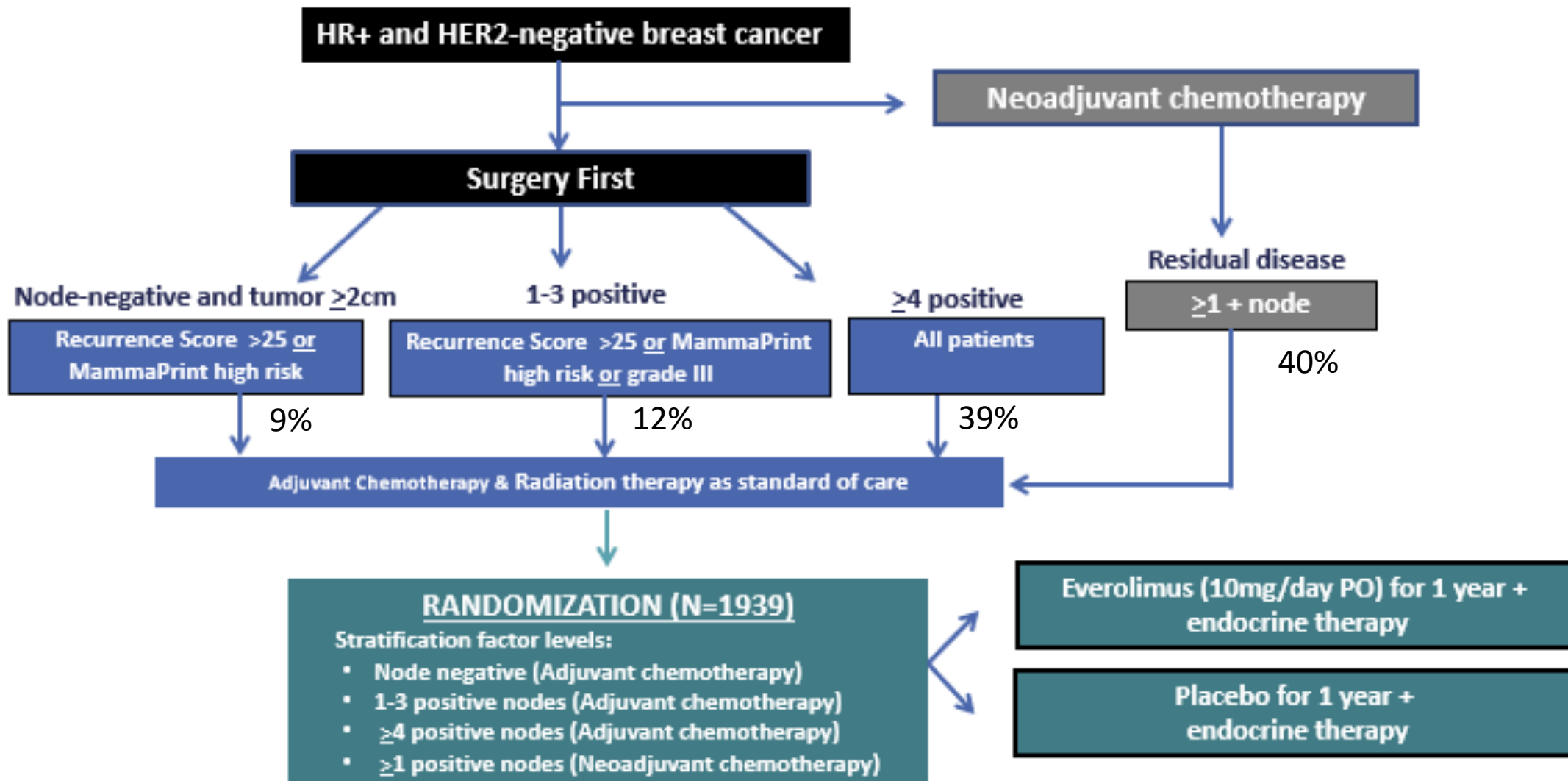
IDFS in cohort 1:  
Impact of **KI-67**



KI67 is **prognostic**, but not ~~predictive~~ of abemaciclib benefit  
'Abemaciclib works in high and low KI67'!

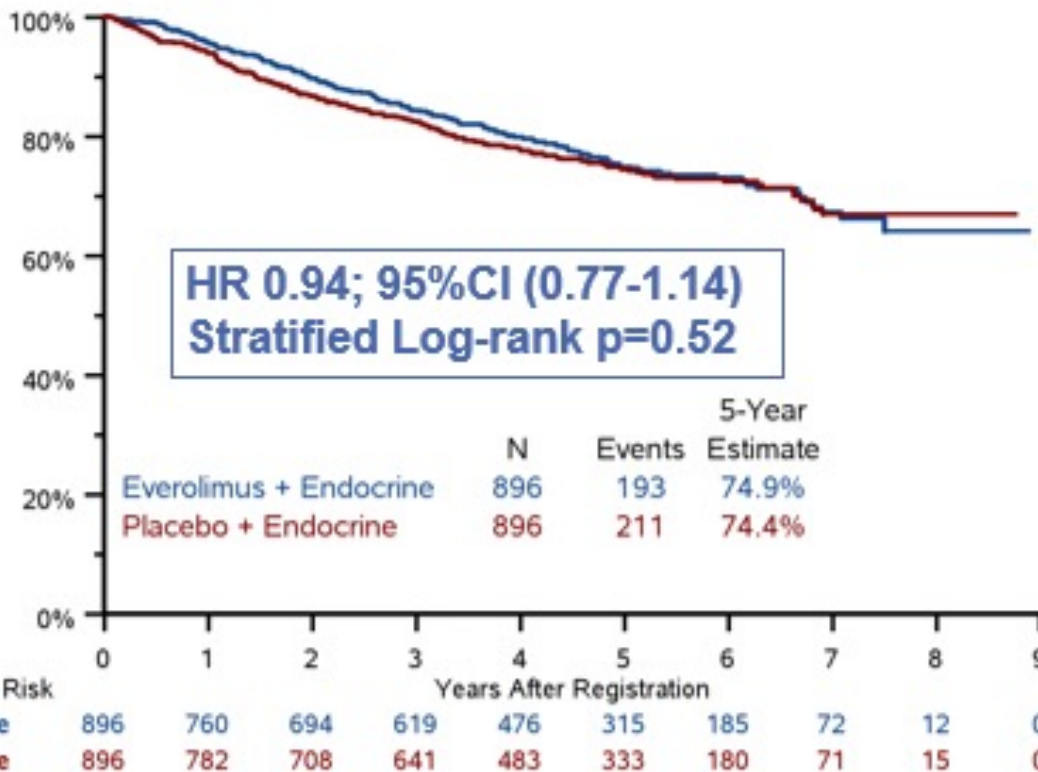


# Adjuvant everolimus: SWOG S1207



# Adjuvant everolimus: SWOG S1207

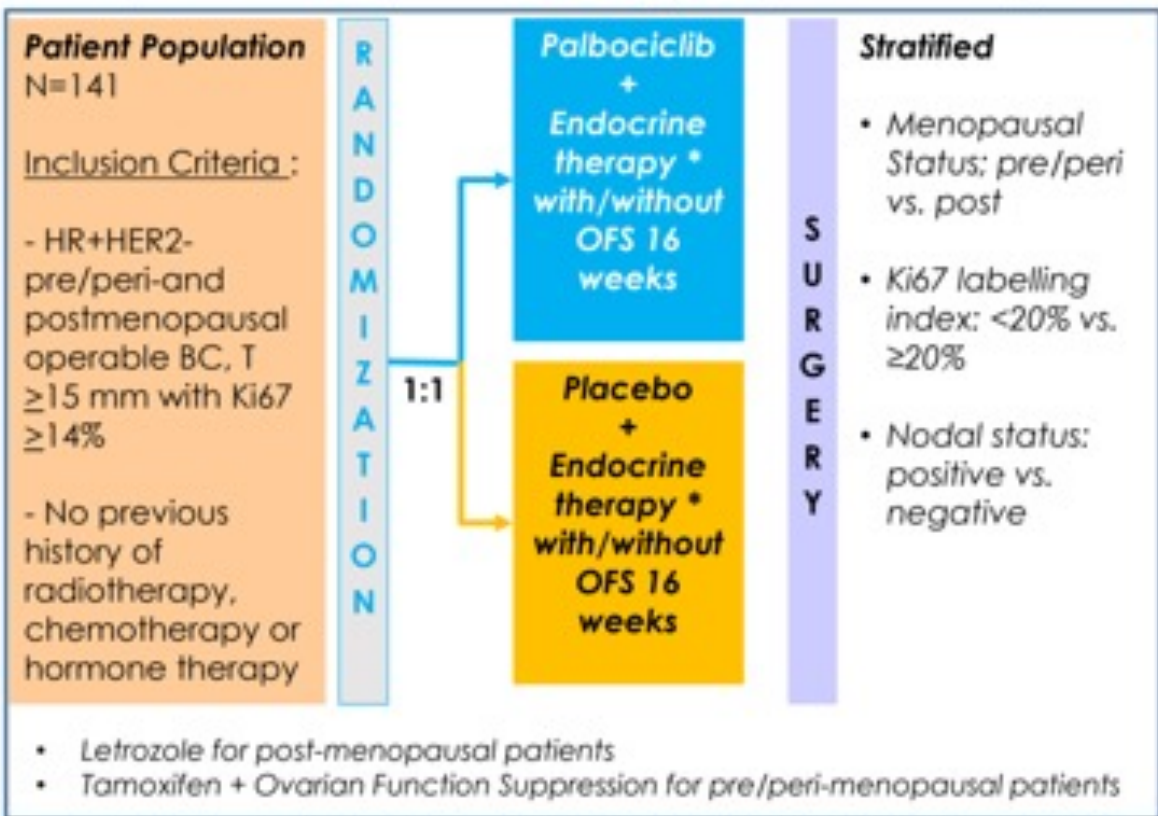
## Invasive Disease Free survival (IDFS)



- Treatment completed 73% (placebo) vs 48% (everolimus)
- Grade  $\geq 3$  35% vs 7%
- Overall Survival HR 0,97 (p0,84)
- IDFS HR 1,08 (p0,52) in postM and 0,64 (p0,02) in **preM** (exploratory)
- OS HR 1,19 (p0,25) in postM and 0,49 (p0,01) in **preM** (exploratory)

Addition of 1y adjuvant everolimus does **not improve** IDFS or OS.  
Potential benefit in **premenopausal** pts?

# Neoadjuvant Palbociclib in ER+/HER2- BC



PEPI score (Preoperative Endocrine Prognostic Index)

Characteristic	Risk	Palbociclib + hormone therapy (N=66)	Placebo + hormone therapy (N=60)	p-value [a]
PEPI Score		n= 66	n= 60	0.563
	low	10 (15.2)	8 (13.3)	
	med	33 (50.0)	33 (55.0)	
	high	23 (34.8)	19 (31.7)	

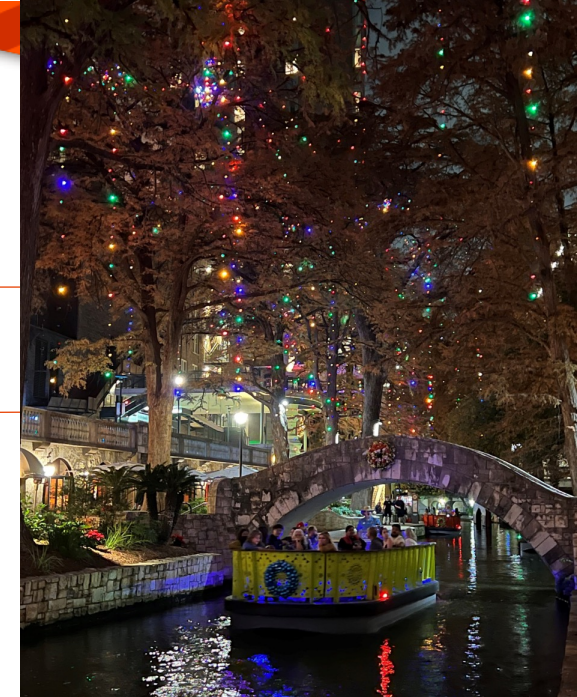
Also no clear differences in clinical response rate and low KI67 after neoadjuvant systemic therapy

Neoadjuvant endocrine therapy **without** CDK4/6i still standard



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  - Neoadjuvant olaparib
- **HER2+:**
  - **APT update** (paclitaxel trastuzumab)



# TAILORx (Oncotype Dx in pN0): 12y update

## Key Eligibility Criteria

- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)

Preregister – Oncotype DX RS (N=11,232)

Register (N=10,273)

## Statistical Design

- Non-inferiority - IDFS
- HR 1.332 (90 vs. 87% 5-yr DFS)
- Type I 10%, type II 5%
- Full info– 835 IDFS events

ARM A: Low RS 0-10  
(N=1619 evaluable)  
ASSIGN

Endocrine Therapy (ET)

Mid-Range RS 11-25  
(N=6711 evaluable)  
RANDOMIZE

Stratification Factors:

Menopausal Status, Planned Chemotherapy,  
Planned Radiation, and RS 11-15, 16-20, 21-25

ARM D: High RS 26-100  
(N=1389 evaluable)  
ASSIGN

ET + Chemo

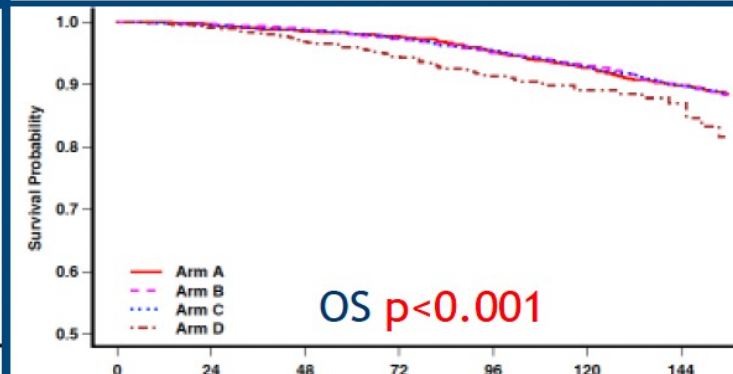
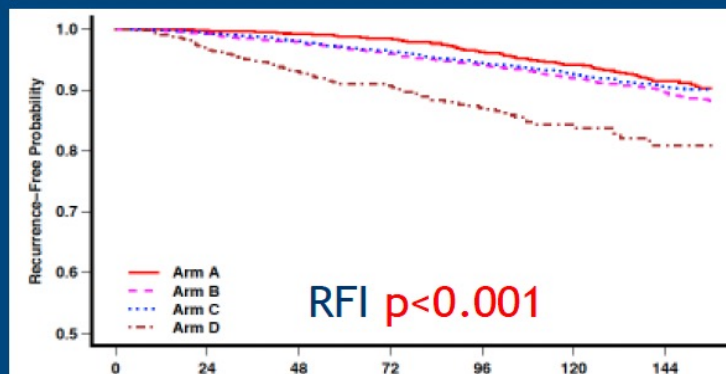
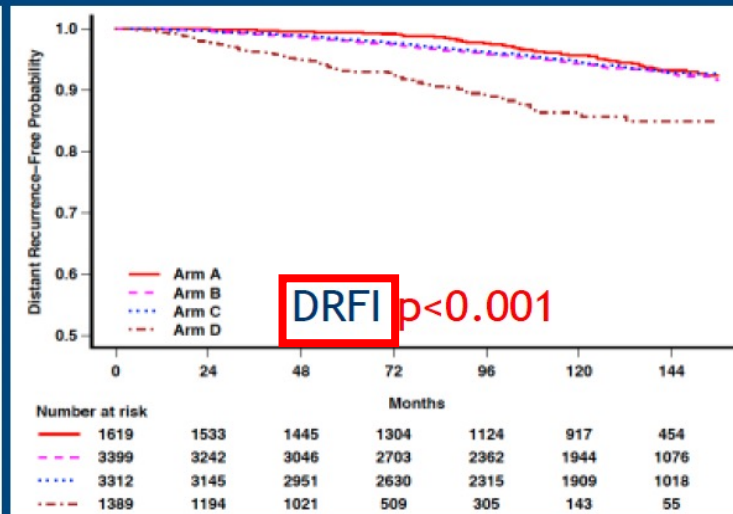
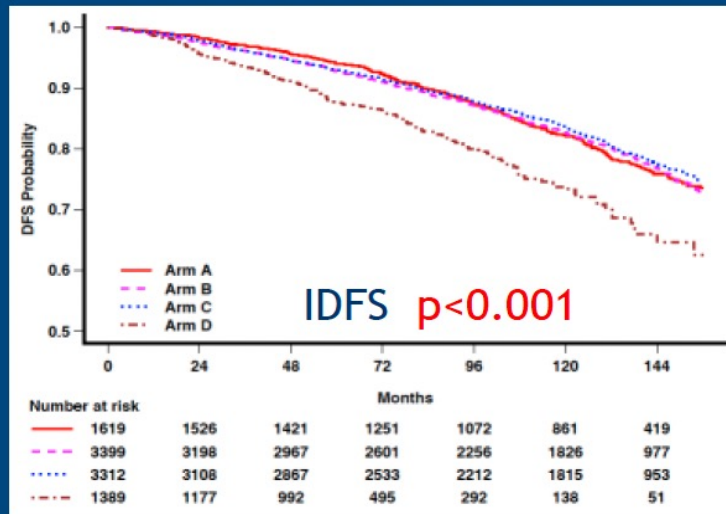
ARM B: Experimental Arm  
(N=3399)  
ET Alone

ARM C: Standard Arm  
(N=3312)  
ET + Chemo



# TAILORx (Oncotype Dx in pN0): 12y update

## TAILORx: Updated Analysis- Kaplan-Meier Curves in All Arms (ITT population)



### 12-Year Event Rates (N=9719)

- RS prognostic for all endpoints
- RS 0-10 (Arm A) – ET Alone
  - DFRI rate: 93.2% (SE 0.8)
  - RFI rate: 91.4% (SE 0.9)
- RS 11-25 (Arms B & C) – ET vs. CET
  - < 1 % difference for all endpoints
    - IDFS: 76.8 vs. 77.4%
    - DRFI: 92.6 vs. 92.8%
    - RFI: 89.6 vs. 90.4%
    - OS: 89.8 vs. 89.8%
- RS 26-100 (Arm D) – CET
  - DFRI rate: 84.8% (SE 1.8)
  - RFI rate: 80.9 (SE 2.2)

- RS 11-25: endocrineR/ non-inferior to chemo+endocrineR/
- Distant Relapse persists >5y (7% distant recurrence at 12y in arm A/B/C)
- RS 26-100 has worst prognosis

# TAILORx (Oncotype Dx in pN0): 12y update in ≤50y

12-year DRFI in ≤50y and RS 16-25

	Estimated Absolute Chemo Benefit <u>Not Stratified</u> by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit <u>Stratified</u> by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (+SE 2.1%)	Low	671 (76%)	Δ -0.5% (+SE 2.2%)
		High	215 (24%)	Δ +3.1% (+SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (+SE 3.4%)
		High	157 (33%)	Δ +11.7% (+SE 7.2%)

In ≤50y:

- Clear chemo benefit in RS 21-25
- Some chemo benefit in RS 16-20 and clinical high risk

Low risk = gr III ≤1cm, gr II ≤2cm, gr III ≤3cm

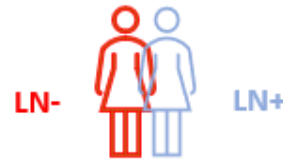
# Mammaprint use for extended endocrine therapy

(EET)



Can forego chemotherapy

Low Risk



Need chemotherapy

High Risk

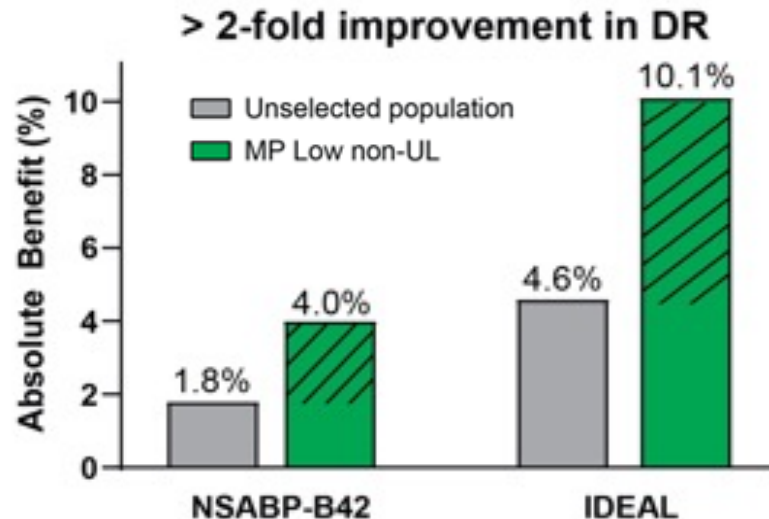


very low recurrence late recurrence

high early recurrence

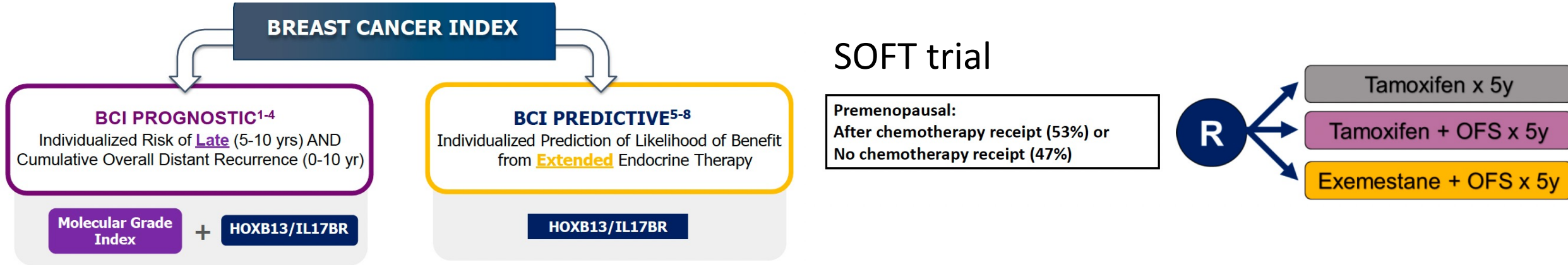
Evaluated in IDEAL trial  
(5 vs 2,5y EET)  
Compared with NSABP-B42 (5 vs 0y EET)

Mammaprint low (not ultra-low) = 43% of IDEAL population



- MammaPrint Low has benefit from EET
- MammaPrint High does **not** have benefit from EET

# Breast Cancer Index (BCI) use for indication OFS

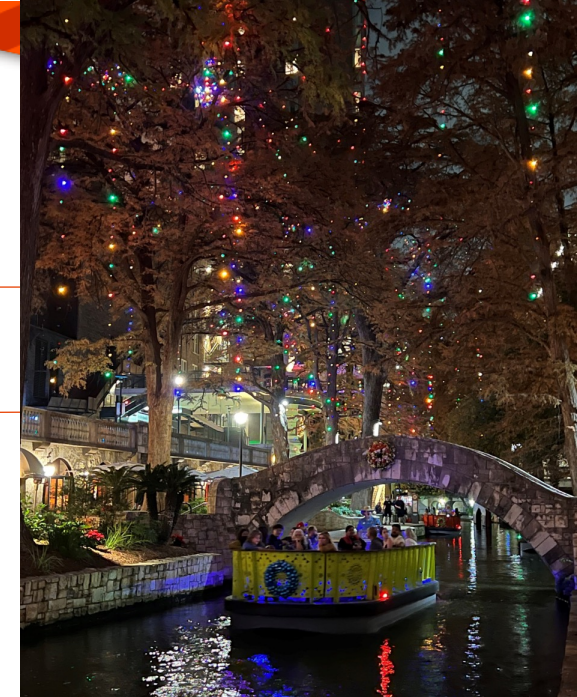


- BCI risk scores were **prognostic** in premenopausal women with HR+ tumors receiving adjuvant endocrine therapy
  - **High** BCI risk scores associated with worse outcome
- BCI (H/I) was **predictive** of OFS (ovarian function suppression) benefit
  - Contrary to study hypothesis, BCI (H/I)-**Low** group consistently derived clinically meaningful benefit while BCI (H/I)-High group did not



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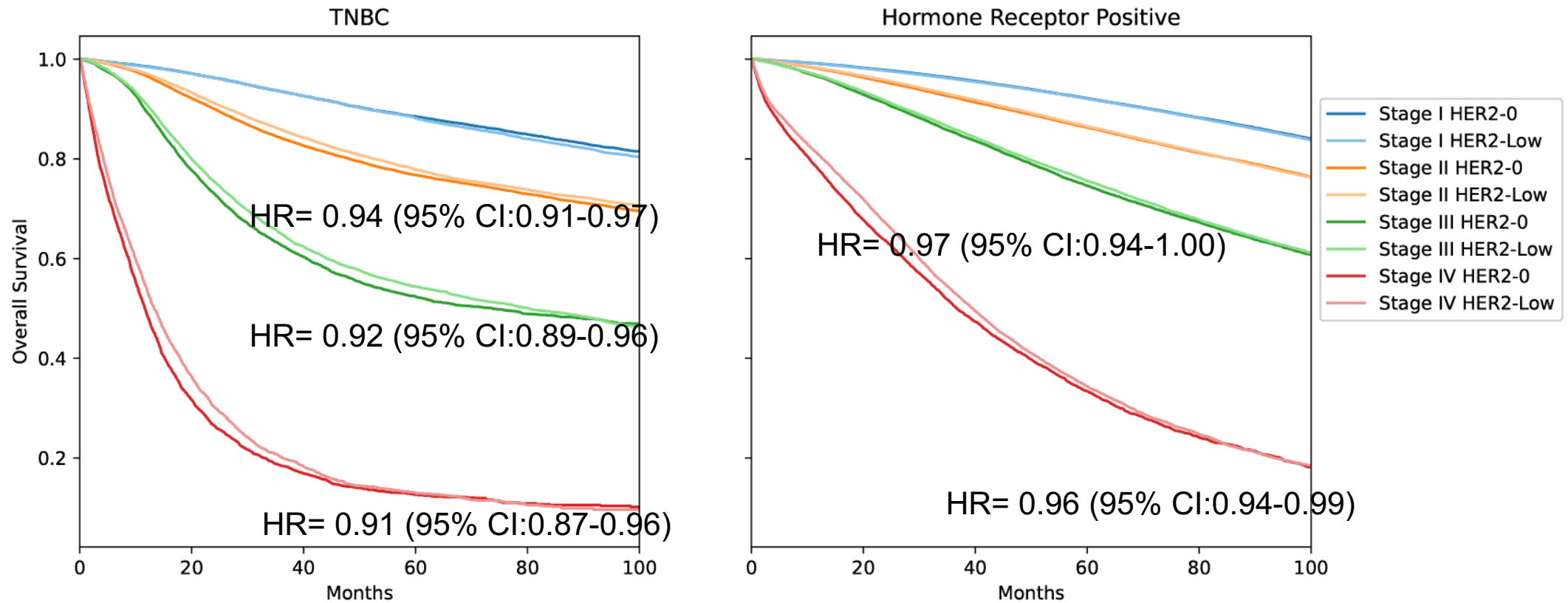


# HER2-low: impact on survival in early BC

## Overall Survival Outcomes: HER2-low vs HER2 0

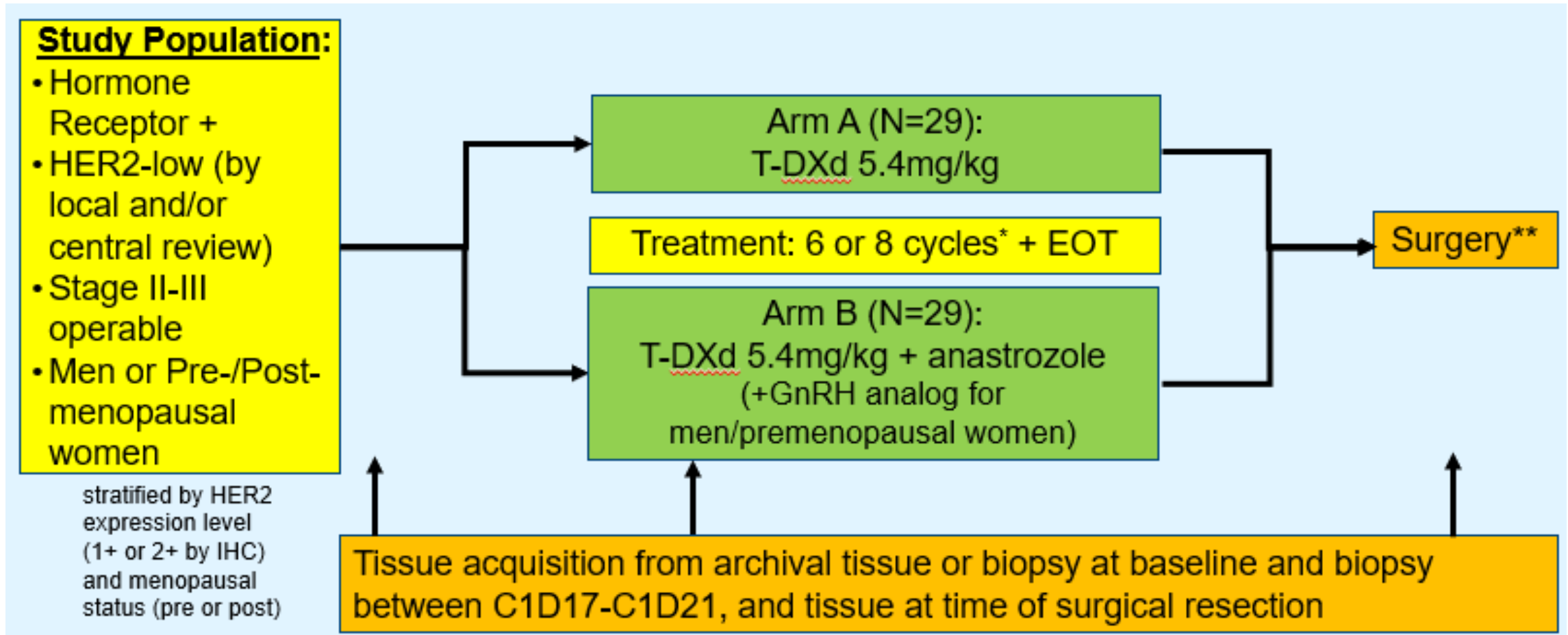
Retrospective Cohort Study: National Cancer Data Base (2010-2019)

N=1,136,016



Overall survival of pts with HER2-low early BC not different compared to HER2 0

# Trastuzumab Deruxtecan (TDXd) neoadjuvant HER2-low



# Trastuzumab Deruxtecan (TDXd) neoadjuvant HER2+

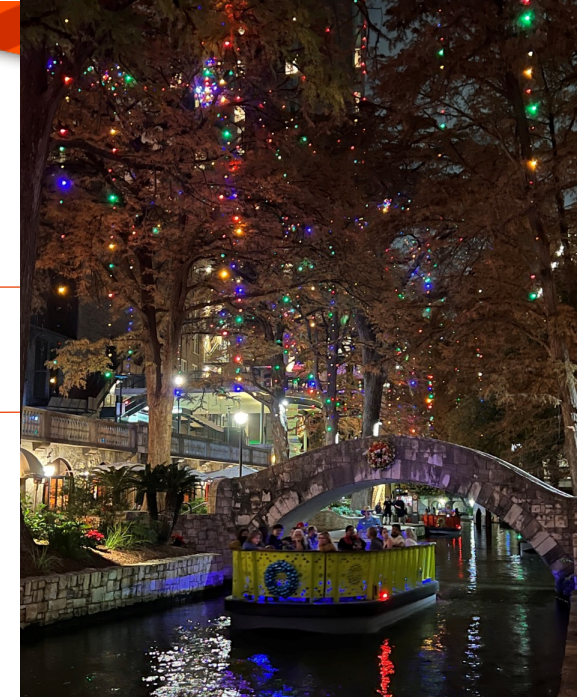
Cycles	Stage at Baseline	Arm A (T-DXd) N=22*				Arm B (T-DXd+Anastrozole) N=20**			
		RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	Stage IIA	0	1 (5%)	2 (9%)	0	0	1 (5%)	6 (30%)	0
	Stage IIB	0	1 (5%)	4 (18%)	2 (9%)	0	0	3 (15%)	1 (5%)
	Stage IIIA	0	0	1 (5%)	2 (9%)	0	0	1 (5%)	1 (5%)
	Stage IIIB	0	0	1 (5%)	0	0	0	0	0
8 Cycles	Stage IIA	0	0	2 (9%)	0	0	1 (5%)	1 (5%)	0
	Stage IIB	0	0	1 (5%)	1 (5%)	0	0	2 (10%)	0
	Stage IIIA	1 (5%)	0	0	0	0	1 (5%)	0	0
	Stage IIIB	0	0	0	0	0	0	0	0

**As of data cutoff 11/25/2022: surgical outcomes pending for 24% (7/29) patients being treated in Arm A and 31% (9/29) in Arm B.**

- Response rate 68% (TDXd) and 58% (TDXd + anastrozole)
- RCB 0/1 15% in both arms, anastrozole does not give additional benefit
- Not ready for clinical practice

## Overview early breast cancer systemic therapy

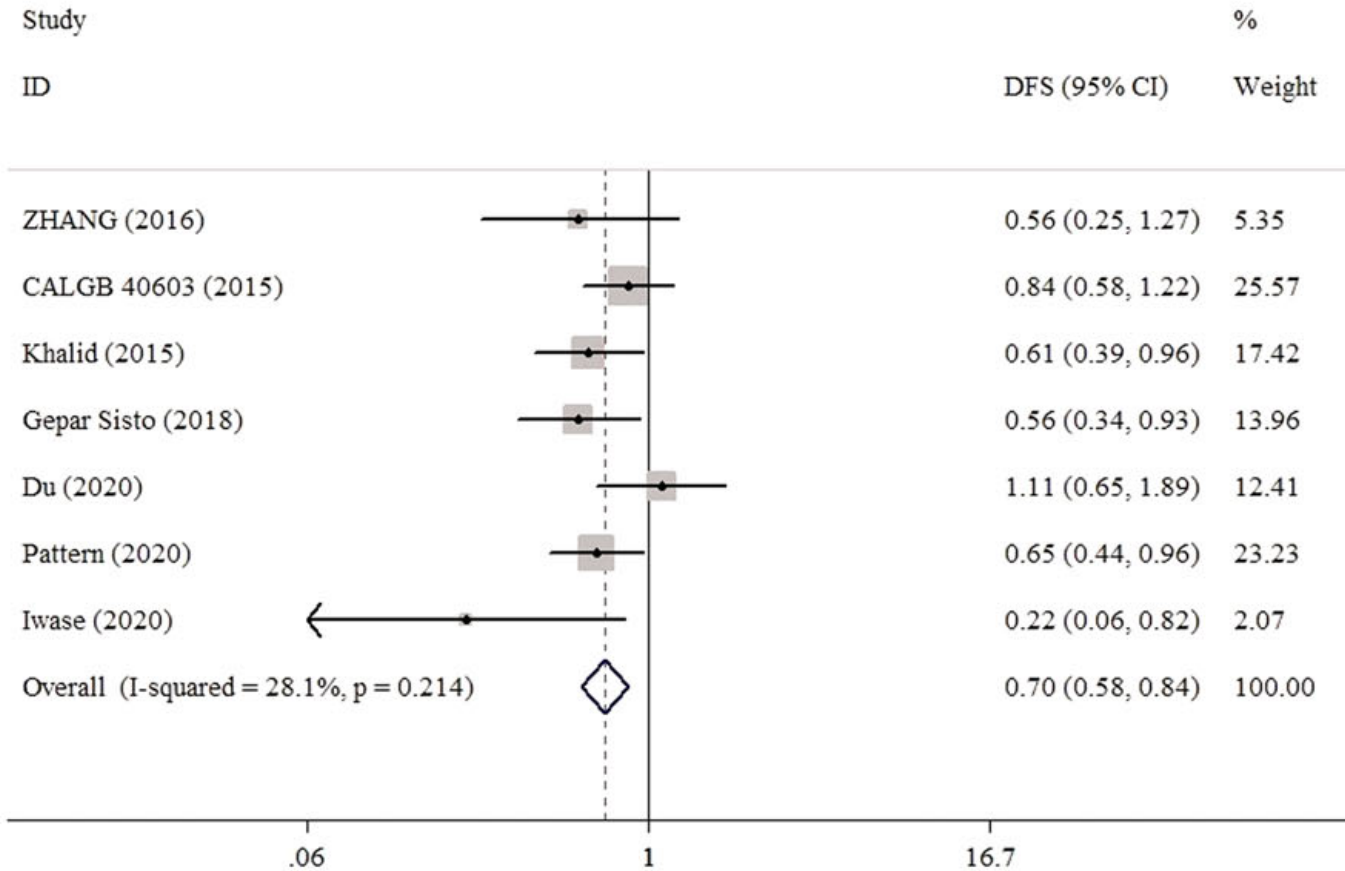
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# (Neo)adjuvant Platinum in TNBC

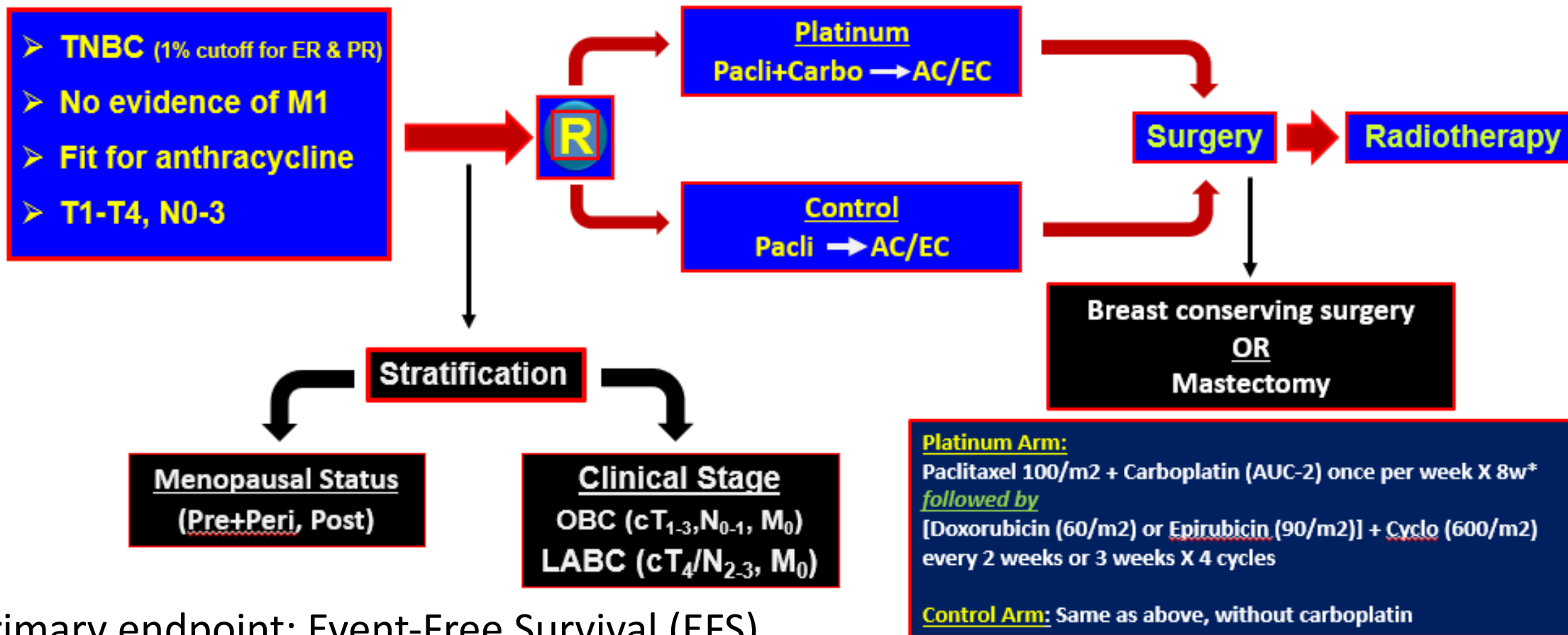
## Meta-analysis of randomised trials



Subgroup	HR (DFS)
Neoadjuvant	0.67 (0.51-0.88)
Adjuvant	0.72 (0.56-0.93)
N0	0.76 (0.50-1.15)
N+	0.71 (0.44-1.15)



# Neoadjuvant Platinum in TNBC



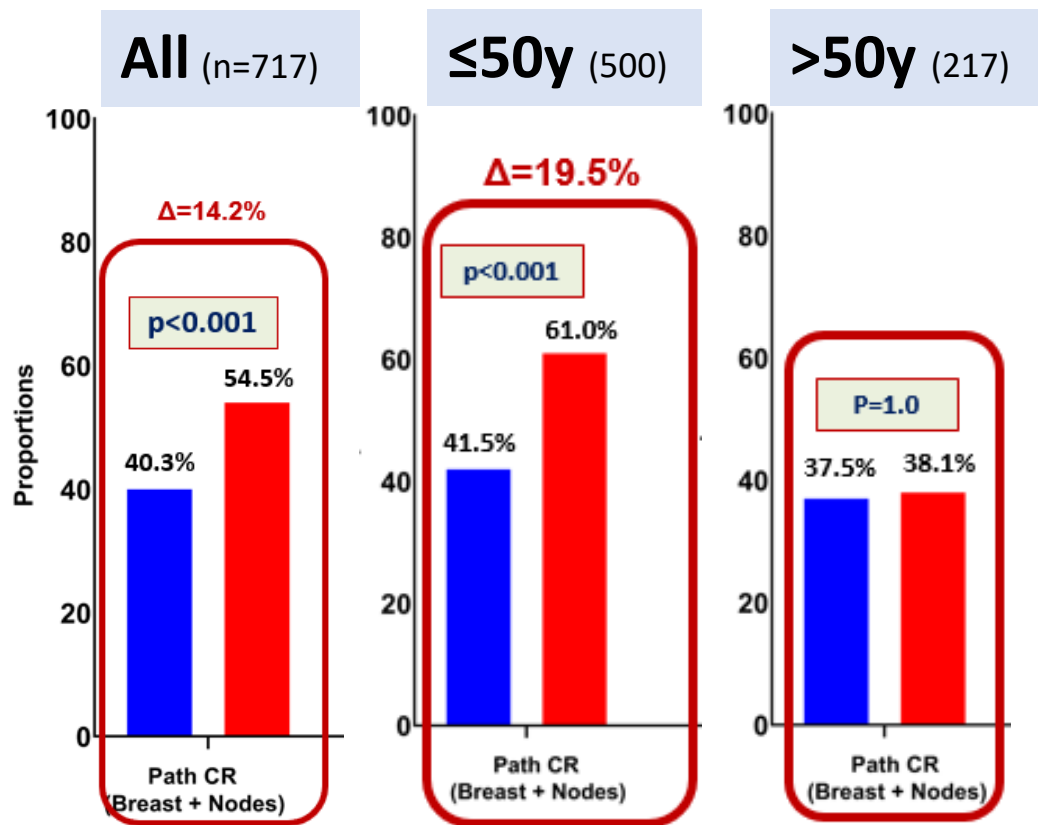
Primary endpoint: Event-Free Survival (EFS)

70% ≤50y, 60% cT4/N2-3

# Neoadjuvant Platinum in TNBC

Pathological complete response (pCR)

Event-Free (EFS) and Overall Survival (OS)



	≤50y			>50y		
	Platinum	Control	Δ	Platinum	Control	Δ
5y-EFS	74,2%	61,7%	<b>12,5%</b>	62,0%	69,3%	7,3%
5y-OS	77,1%	65,9%	<b>11,2%</b>	68,0%	68,9%	0,9%

- Neoadjuvant platinum in TNBC mainly beneficial in ≤50y
- No info on BRCA status in this trial

# Neoadjuvant Platinum in TNBC

## Toxicity

Toxicity	Platinum (N=361)	Control (N=356)	Platinum (N=361)	Control (N=356)
	<u>Any</u> <u>Grade</u>		<u>Grade III or</u> <u>Worse</u>	
Neutropenia	56 (15.5%)	18 (5.1%)	31 (8.6%)	7 (2.0%)
Anemia	23 (6.4%)	9 (2.5%)	7 (1.9%)	1 (0.3%)
Thrombocytopenia	21 (5.8%)	4 (1.1%)	7 (1.9%)	0 (0%)
Neutropenic Fever	-	-	16 (4.4%)	10 (2.8%)
Nausea	24 (6.6%)	26 (7.3%)	0 (0%)	1 (0.3%)
Vomiting	37 (10.2%)	34 (9.6%)	1 (0.3%)	1 (0.3%)
Diarrhea	22 (6.1%)	16 (4.5%)	4 (1.1%)	3 (0.8%)
Mucositis	21 (5.8%)	21 (5.9%)	1 (0.3%)	3 (0.8%)
Peripheral Neuropathy	65 (18.0%)	65 (18.3%)	3 (0.8%)	3 (0.8%)
Skin	10 (2.8%)	15 (4.2%)	3 (0.8%)	3 (0.8%)
Hepatic	1 (0.3%)	2 (0.6%)	0 (0%)	0 (0%)
Any SAE	53 (14.7%)	46 (12.9%)		

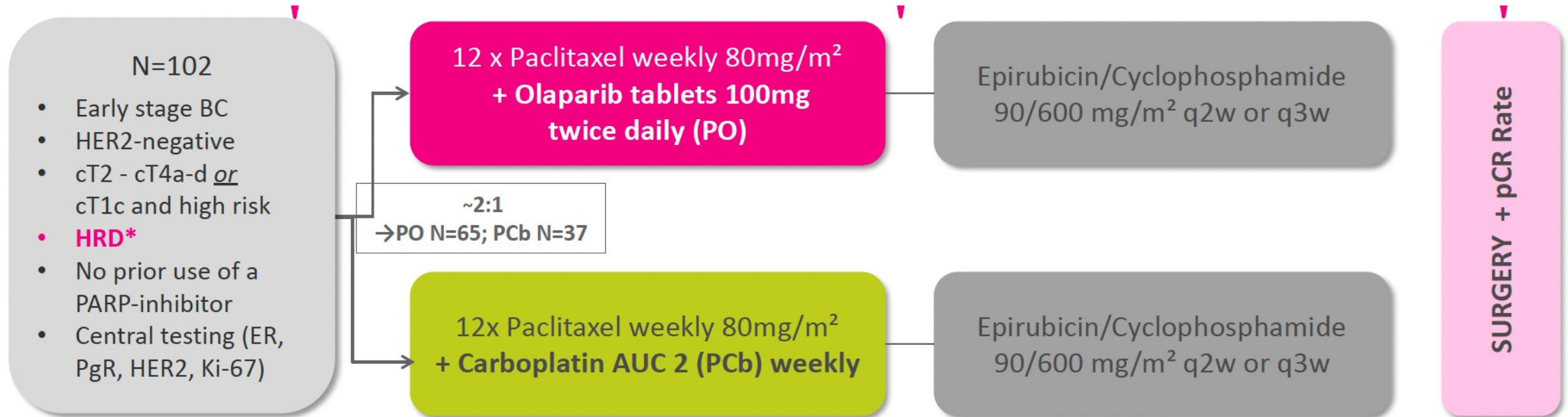
## Treatment completion

	Platinum (N=361)	Control (N=356)
<i>Completed 8 cycles of</i> Weekly Paclitaxel or Weekly Paclitaxel-Carboplatin	341 (94.5%)	346 (97.2%)

- Increased haematological toxicity
- No increased non-haematological toxicity
- No impact on treatment completion
- No difference young vs old

# Neoadjuvant Olaparib in HER2- BC with HRD

## GEPAROLA trial



### Stratification Factors:

- Age (<40 years vs >= 40 years)
- Hormone Receptor Status (HR+ vs HR-)

\* Patients with either a known somatic or germline *BRCA1/2* mutation or HRD score<sup>1</sup> high (defined as a MyChoice™ Score of ≥42)

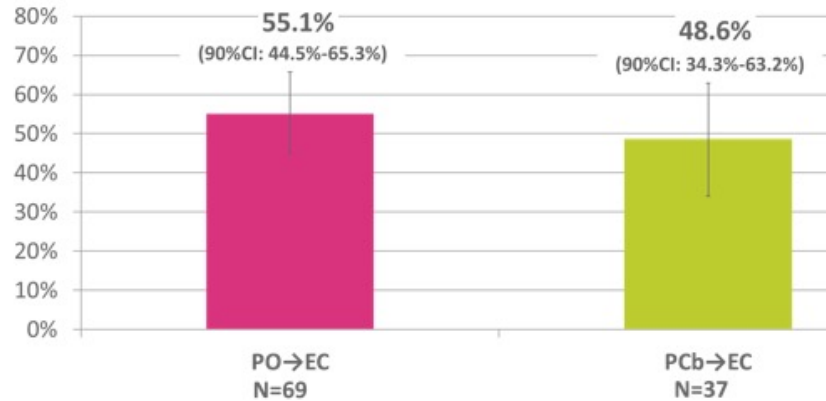
Fasching et al. Ann Oncol. 2020  
<sup>1</sup>Timms et al. Breast Cancer Res 2014

cN+ 32%, ER+ 27%, gBRCAm 56%

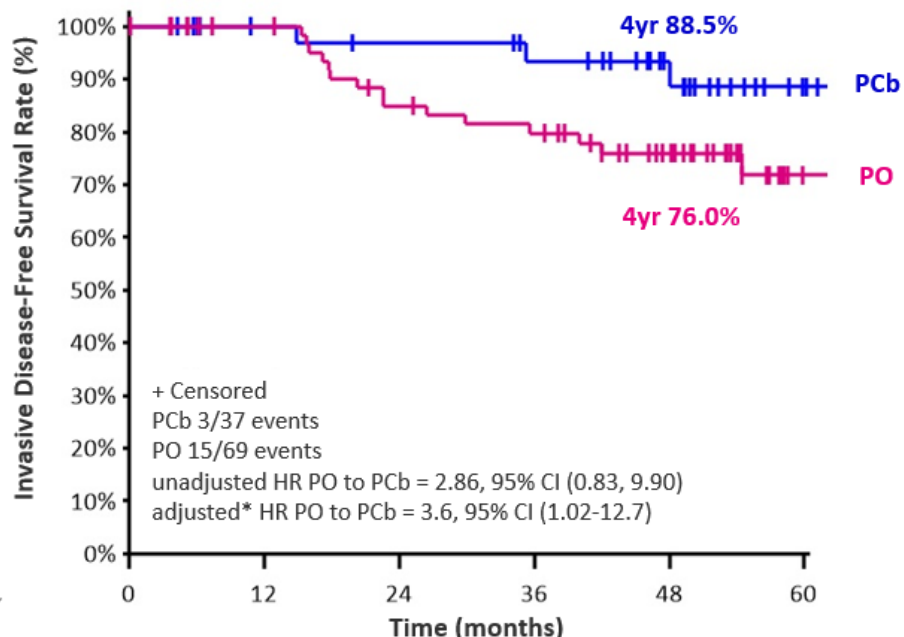


# Neoadjuvant Olaparib in HER2- BC with HRD

Pathological complete response (pCR)



Invasive Disease Free Survival (iDFS)

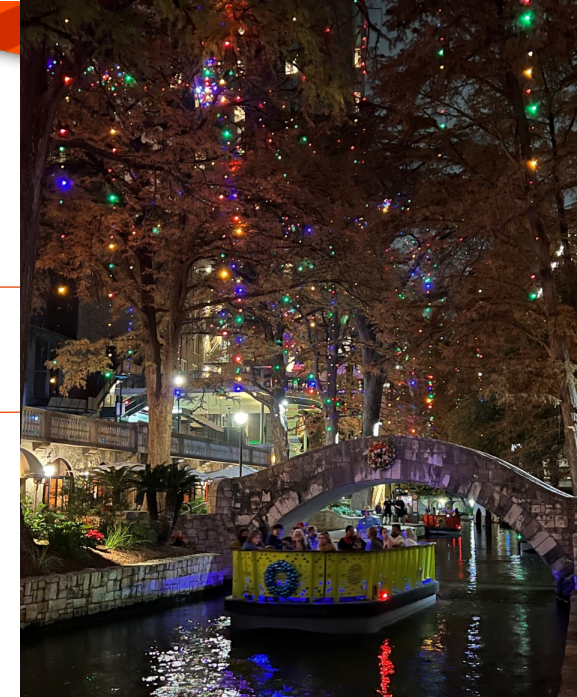


- No difference in g/tBRCAm
- Big difference in g/tBRCA **wildtype** (HRD score high)
- 4y DDFS numerically worse (81,2% vs 93,4%)
- 4y OS numerically worse (89,2% vs 96,9%)

- Neoadjuvant Olaparib is inferior to platinum for long term outcome
- Hypothesis:
- Olaparib is potentially equivalent to platinum in g/tBRCAm
  - Olaparib is inferior to platinum in HRD tumors without g/tBRCAm.

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# HER2+ APT regimen update (12 paclitaxel weekly +1y Trastuzumab)

Even for very early stage HER2+ breast cancer, prognosis is worse than for HER2- without systemic therapy

Series	Outcome	HER2- (N)	HER2+ (N)
MD Anderson <sup>1</sup> T1a/b, N0	5-year relapse free survival	94% (N=867)	77% (N=98)
NCCN <sup>2</sup> T1a/b, N0	5-year disease free survival	89% (N=3127)	83% (N=255)
British Columbia Tumor Registry <sup>3</sup> Stage I	10-year relapse free survival	76% (N=1128)	66% (N=117)

# HER2+ APT regimen update (12 paclitaxel weekly +1y Trastuzumab)

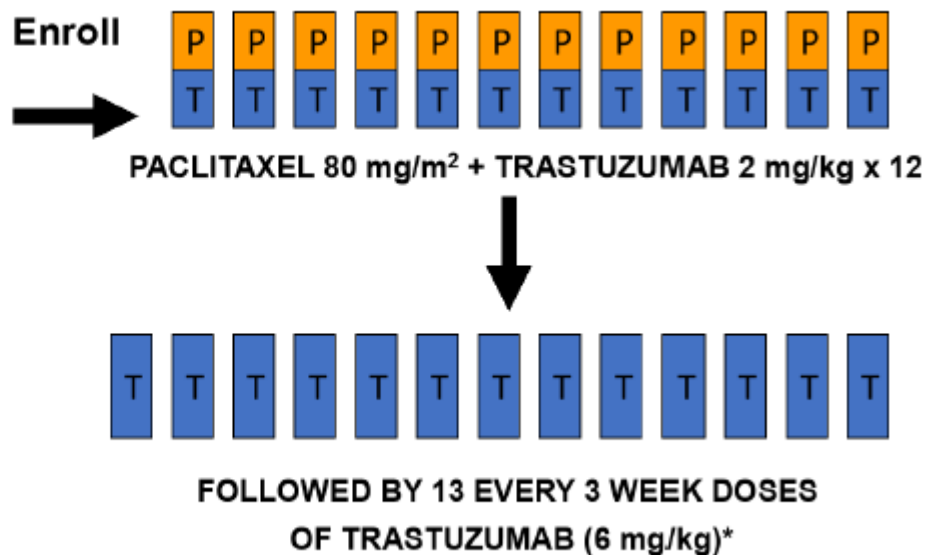
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**HER2+  
ER+ or ER-  
Node Negative  
≤ 3 cm**

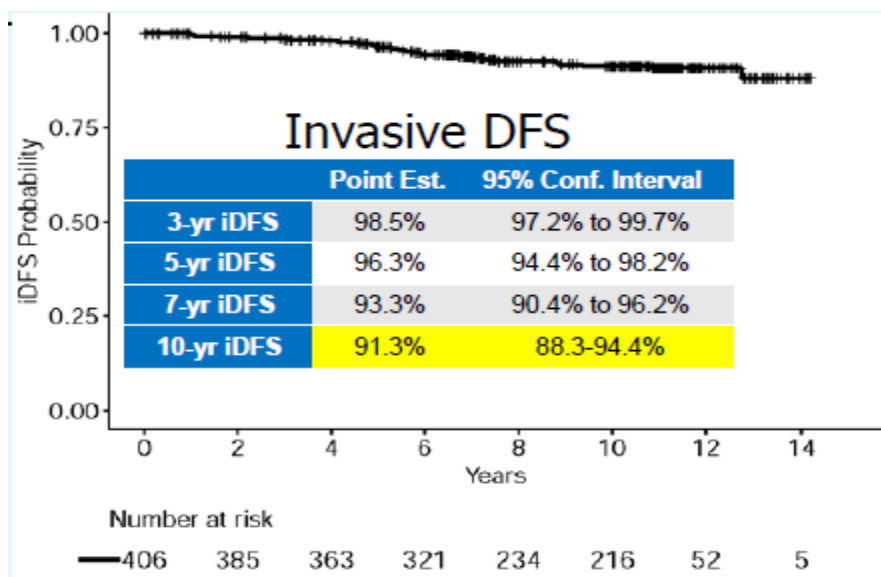
Planned N=400  
Actual: 406

**49% T1a/T1b**  
**42% T1c**  
**9% T2 (≤3 cm)**  
**67% HR positive**

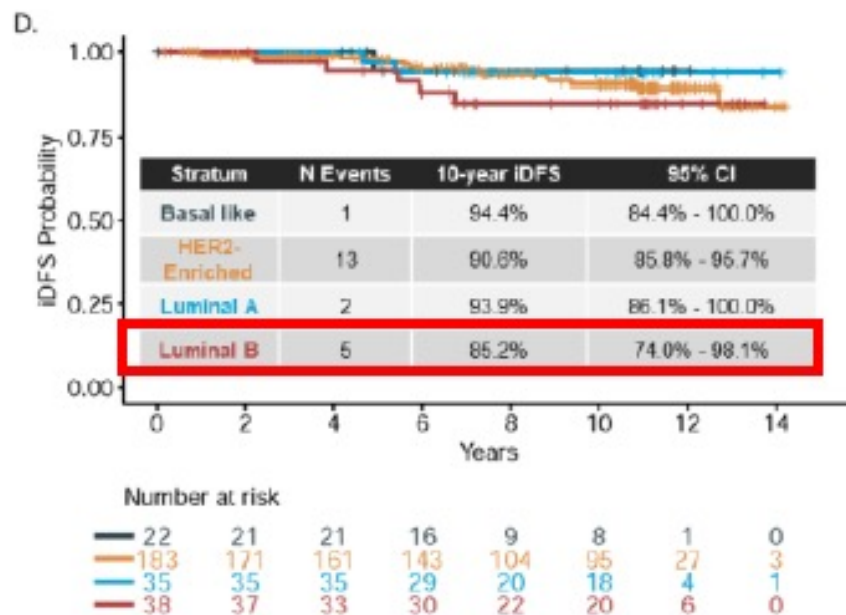




# HER2+ APT regimen update (12 paclitaxel weekly +1y Trastuzumab)



- 31 events (on 406 pts) at 10y FUP
- **6 distant recurrences**
- 6 ipsilateral recurrences
- 9 contralateral new cancers (1 HER2+)
- 10 deaths: 10y BCSS 98,8%



- No impact of ER status
- No impact of TIL level
- **Luminal B** subtype has lower iDFS
- **HER2DX** risk score predicts relapse (optimal cutoff? 50? 32?)

# Take home messages



- Luminal:

- 4y MonarchE update further supports the addition of **adjuvant abemaciclib** to endocrine therapy for patients with HR+, HER2-, node-positive, high-risk EBC (pN2 or pN1 and grade III of  $\geq 5\text{cm}$ )
- Addition of 1y **adjuvant everolimus** does not improve IDFS or OS. Potential benefit in **premenopausal** pts?
- Neoadjuvant endocrine therapy **without CDK4/6i** still standard
- **OncotypeDx** in N0: in RS 0-25, relapse persists  $>5\text{y}$  (7% distant recurrence at 12y).
- **Gene expression profiling** can help to advice for extended endocrine therapy (mammaprint) and ovarian function suppression (BCI)
- **HER2 low**: TDXd +/- anastrozole leads to low pCR rate

# Take home messages



- TNBC:
  - Neoadjuvant **platinum** mainly beneficial in **premenopausal** pts
  - Neoadjuvant **Olaparib** is **inferior** to platinum for long term outcome, especially in those with HRD without g/tBRCAm
- HER2+:
  - **APT regimen** (12w paclitaxel + 1y trastuzumab) has excellent 10y outcome in low stage tumors