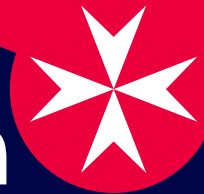
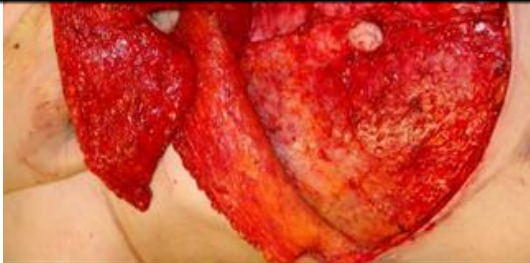
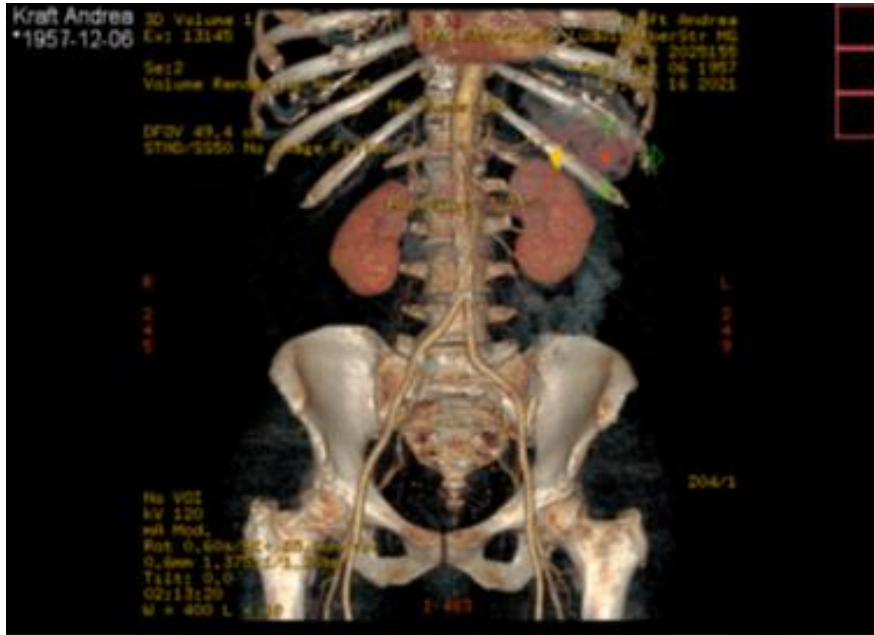


# „Practise changing“ Entwicklungen beim Mammakarzinom

5. Mönchengladbacher Tag der  
Gynäkologie  
Ulrike Nitz  
Brustzentrum Niederrhein



# Neues aus der lokalen Therapie: freie Lappen



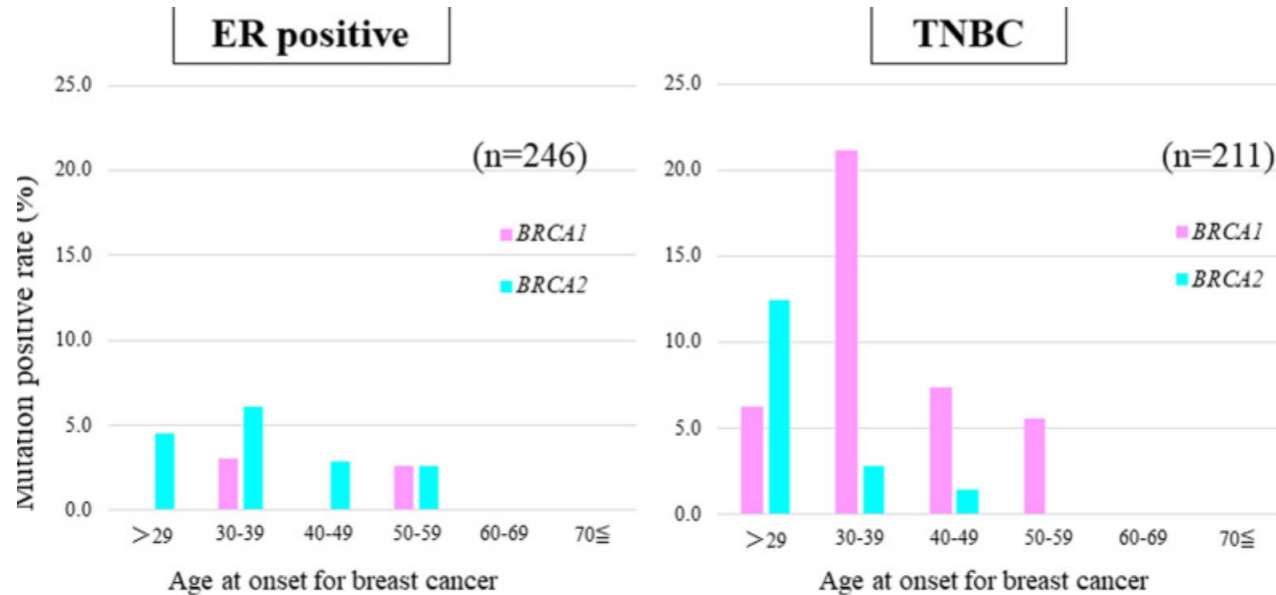
# Neues aus der lokalen Therapie



Patientin \* 1945  
Hohes Narkoserisiko  
Primär M1 (hep, oss)  
Mixed response mit  
Progress lokal



# Triple negatives Mammaca: BRCA Mutation und Alter

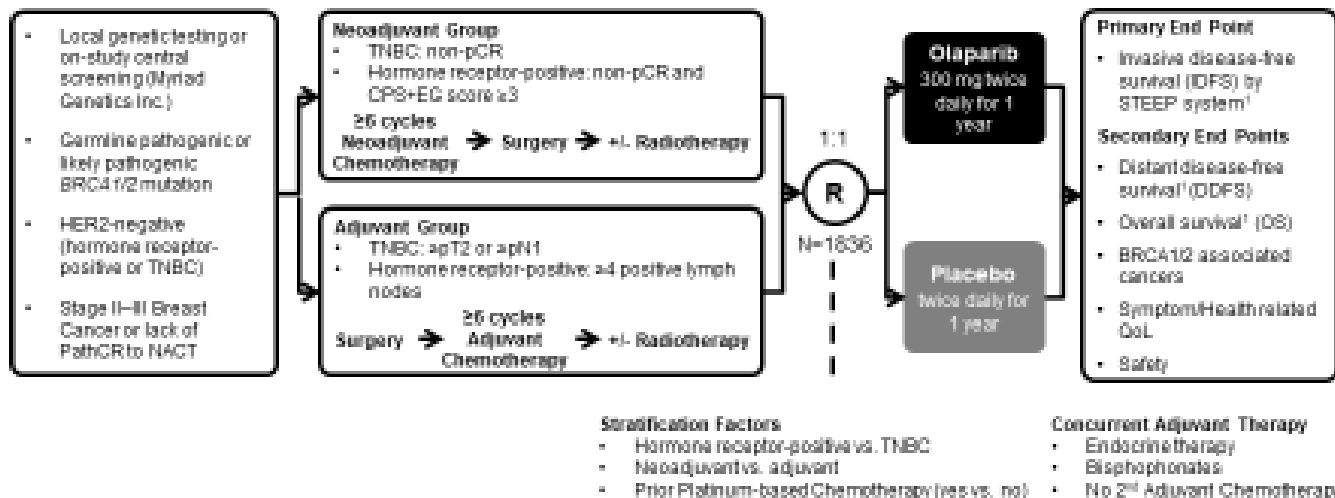


Ohano M. et al  
J Hum Genet 66:307-314, 2021



# Triple negatives Mammakarzinom: BRCA Mutation

## OlympiA – Trial Schema



Hormone receptor +ve defined as ER and/or PgR positive (IHC staining  $\geq 1\%$ ); Triple Negative defined as ER and PgR negative (IHC staining  $< 1\%$ ); <sup>1</sup>Hudis CA, J Clin Oncol 2007

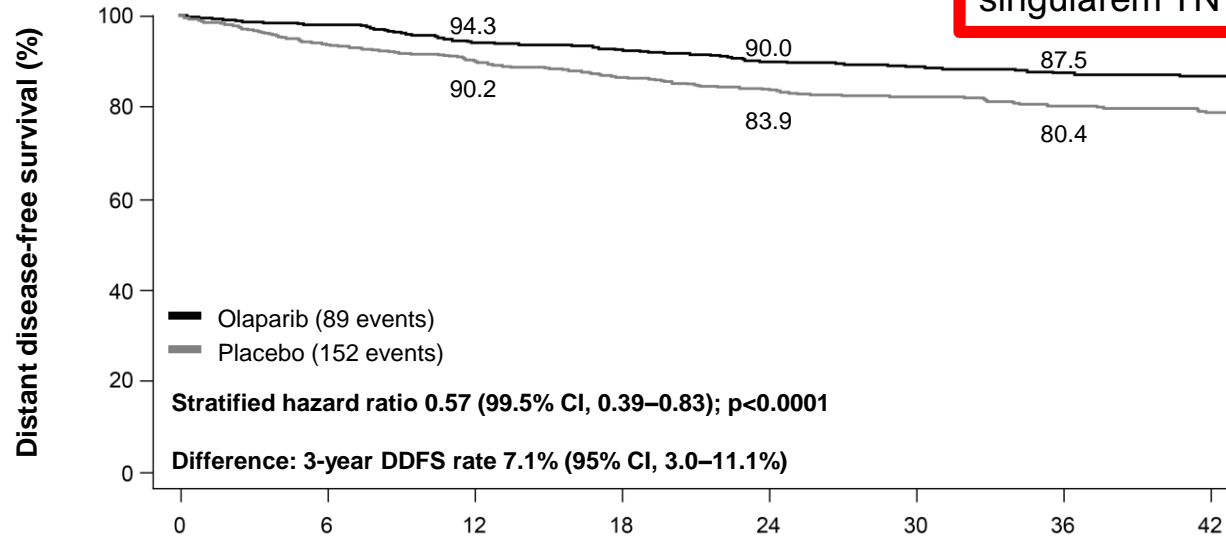


# OlympiA – Results

## Distant disease-free survival

**NEU!!**

Kostenübernahme für BRCA Testung  
für Patientinnen mit  
singulärem TN bis zum 60. Lj möglich

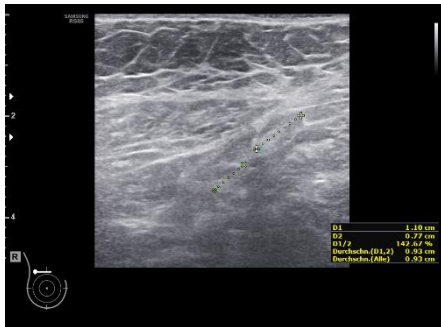
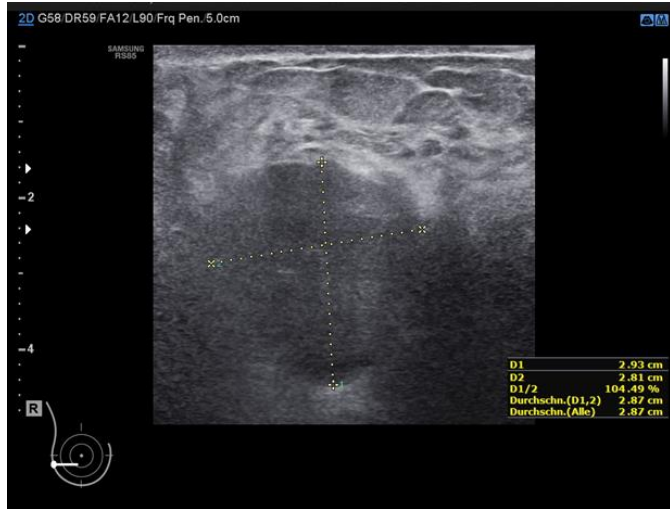


No. at Risk

Time since randomization (months)

Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

# Triple negatives Mammakarzinom: Immuntherapie



KJ \* 1976

6/21 TN MK re unten aussen cT2-3, cN2  
M0

Standard:

NACT mit 4 x EC q2w → 12 x Paclitaxel  
(+ Carboplatin)

Bei pPR Capecitabine für 6-8 Zyklen  
Postadjuvant

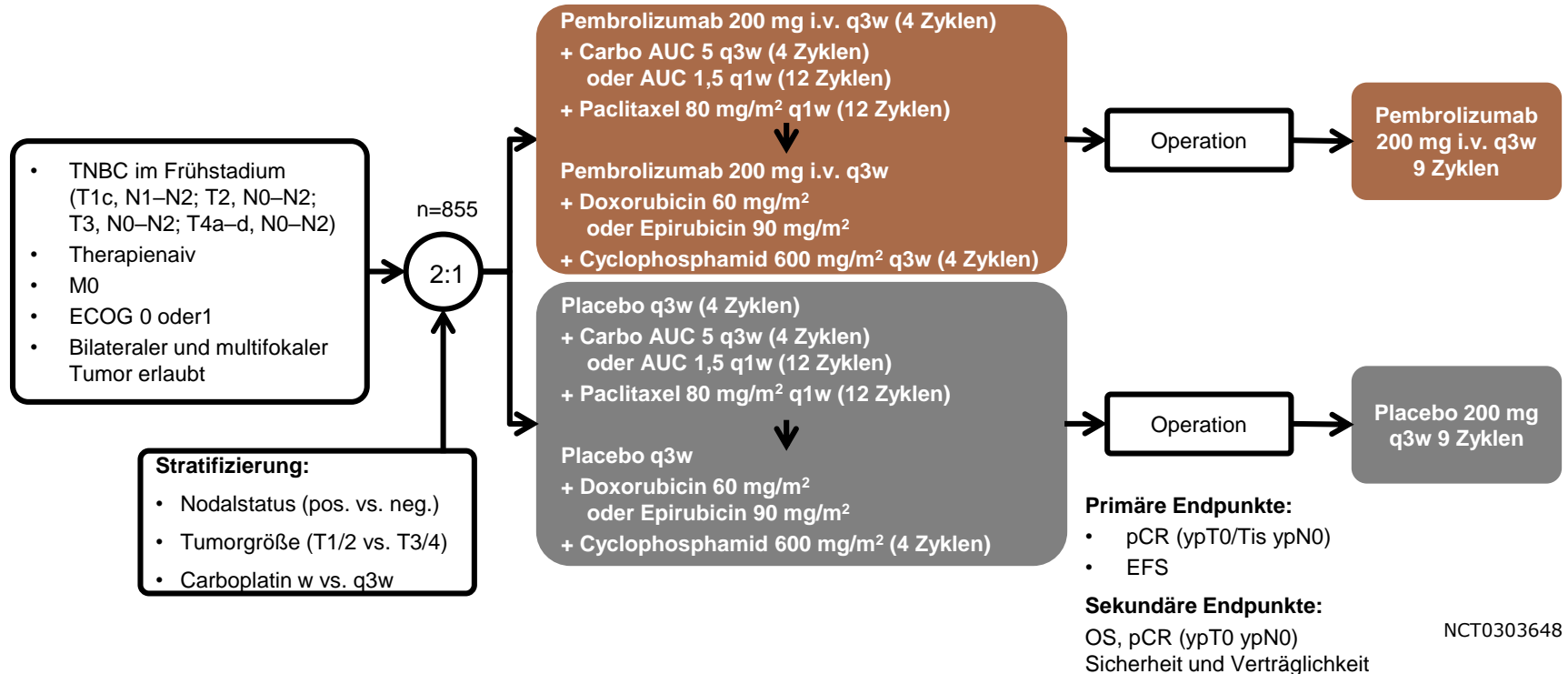
Therapie: (12 x Paclitaxel/Carbo q1w →  
4 x EC q3w) + Pembrolizumab  
(in Anlehnung an die Keynote 522)

12/21 BET + SLN + non SLN → ypT0, ypN0



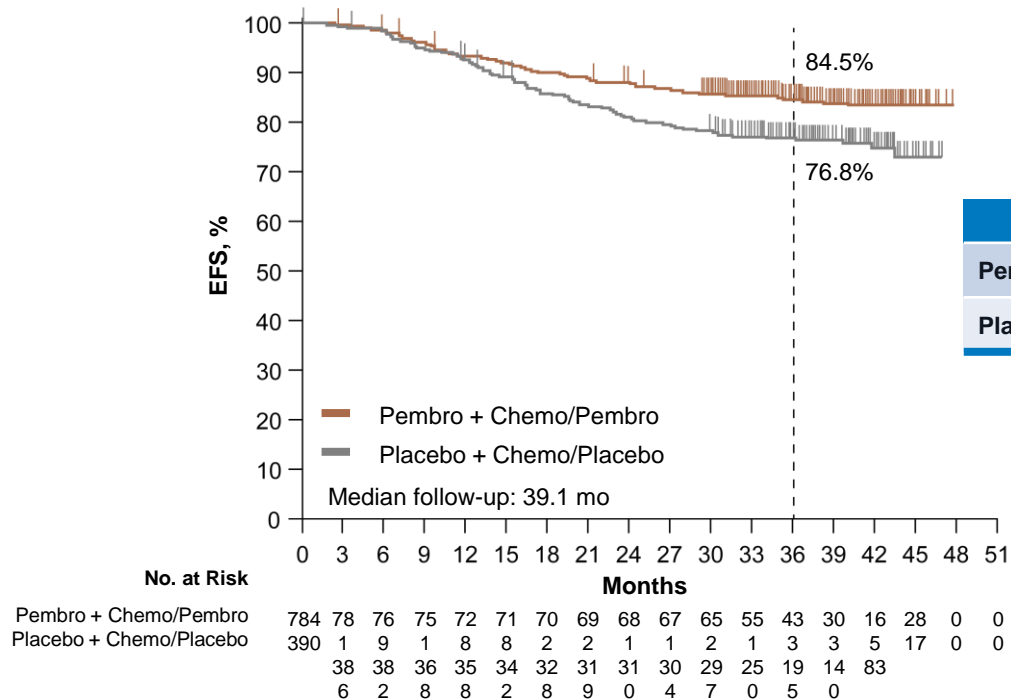
# KEYNOTE-522 – Studiendesign

## Pembrolizumab + CTX neoadjuvant und Pembrolizumab adjuvant bei TNBC





# KEYNOTE-522 – Ereignisfreies Überleben zu IA4



	Events	HR (95% CI)	p-value
Pembro + Chemo/Pembro	15.7%	0.63 (0.48–0.82)	0.00031
Placebo + Chemo/Placebo	23.8%		

# HER2+++ Mammakarzinom: 2 Praxisfälle

## 55 jährige Patientin

- cT2 (2,7 cm), cN0, G3, ER 0%, PR 0%, HER2 3+, Ki-67 35%
- Neoadjuvante Chemotherapie mit 12xPaclitaxel weekly +Pertuzumab+ Trastuzumab
- US, MG und Mamma-MRT nach 12 Wochen: klinische Komplettremission
- BET/SLN
- ypT0, ypN0
- Radiatio, Trastuzumab für 1 Jahr

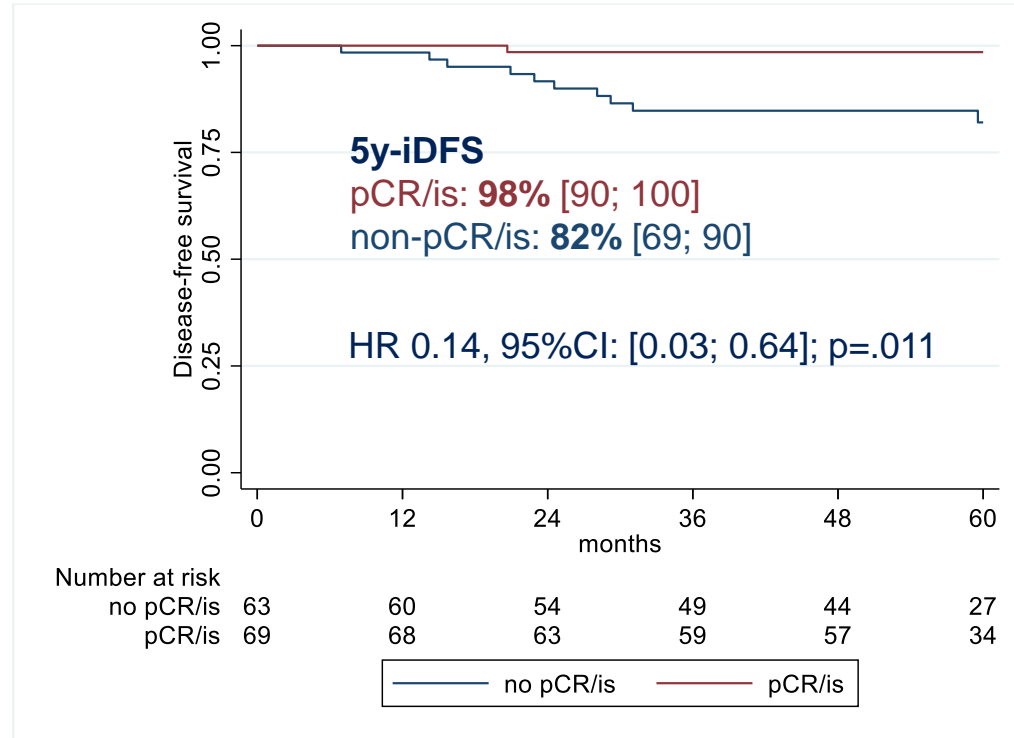
## 65 jährige Patientin

- cT2 (2,7 cm), cN0-1, G2, ER 50%, PR 0%, HER2 3+, Ki-67 25%
- Neoadjuvant 12xPaclitaxel weekly +Pertuzumab+ Trastuzumab, PNP Grad 2
- US nach 12 Wochen: 1,5 cm Residualbefund
- Neoadjuvant 4xEC: 1,1 cm Restbefund
- BET/SLN/SS/Axilladisektion
- ypT1c (12 mm), ypN1 (3 mm LK Metastase/12), R0
- Radiatio Mamma/LAW, T-DM1, ggf. Neratinib
- Oder Teilnahme DESTINY-05 (T-DM1 vs. Trastuzumab Deruxtecan)



# WSG-ADAPT HER2+ /HR-

## iDFS: non-pCR vs pCR

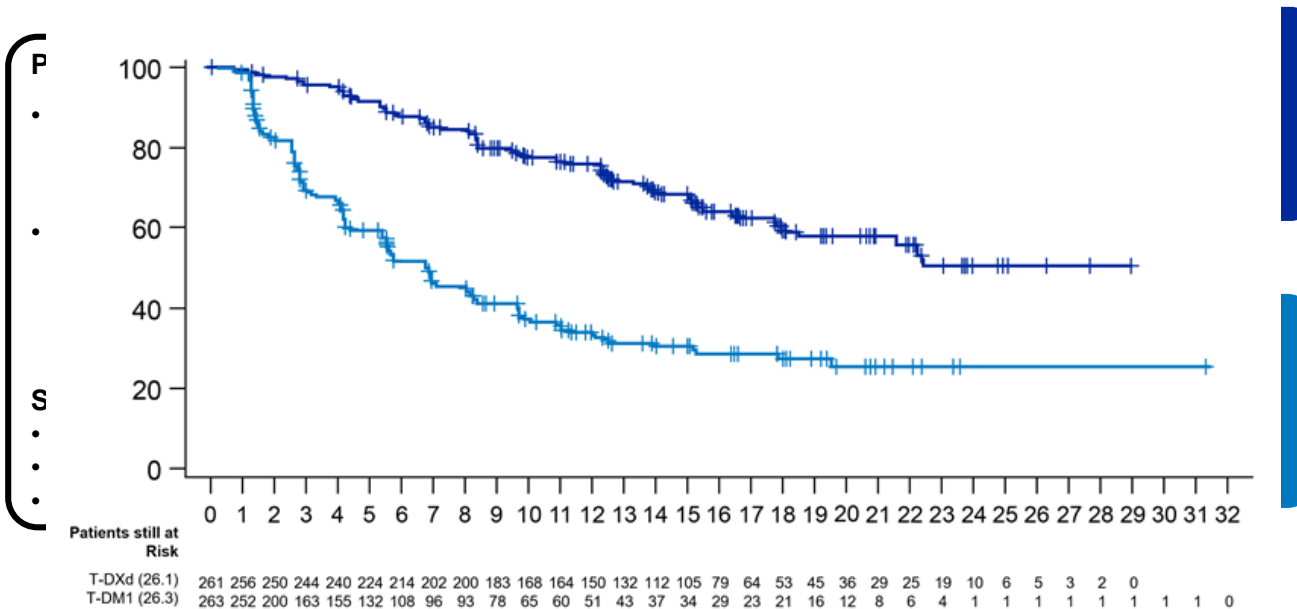


Patients with  
no further CT after pCR

Arm A	Arm B
9 (29.0%)	30 (79.0%)

# DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

## An open-label, multicenter study (NCT03529110)



# HER2 positives Mammakarzinom - seit 1/22 DESTINY 05

DS8201-A-U305: Phase 3 study HER2-positive high-risk post-neoadjuvant eBC

## Key Eligibility:

- eBC with residual disease following neoadjuvant therapy
- Completion of neoadjuvant therapy including trastuzumab followed by surgery
- High-risk of recurrence (node positive or inoperable at presentation)
- Centrally confirmed HER2-positive status
- ECOG PS: 0-1

## Stratification Factors:

- Operative status at presentation (operable, inoperable)
- Tumor hormone receptor status (positive, negative)
- Post-neoadjuvant therapy pathological nodal status (positive, negative)
- HER2-targeted neoadjuvant therapy approach (single, dual)

n = 1600

R

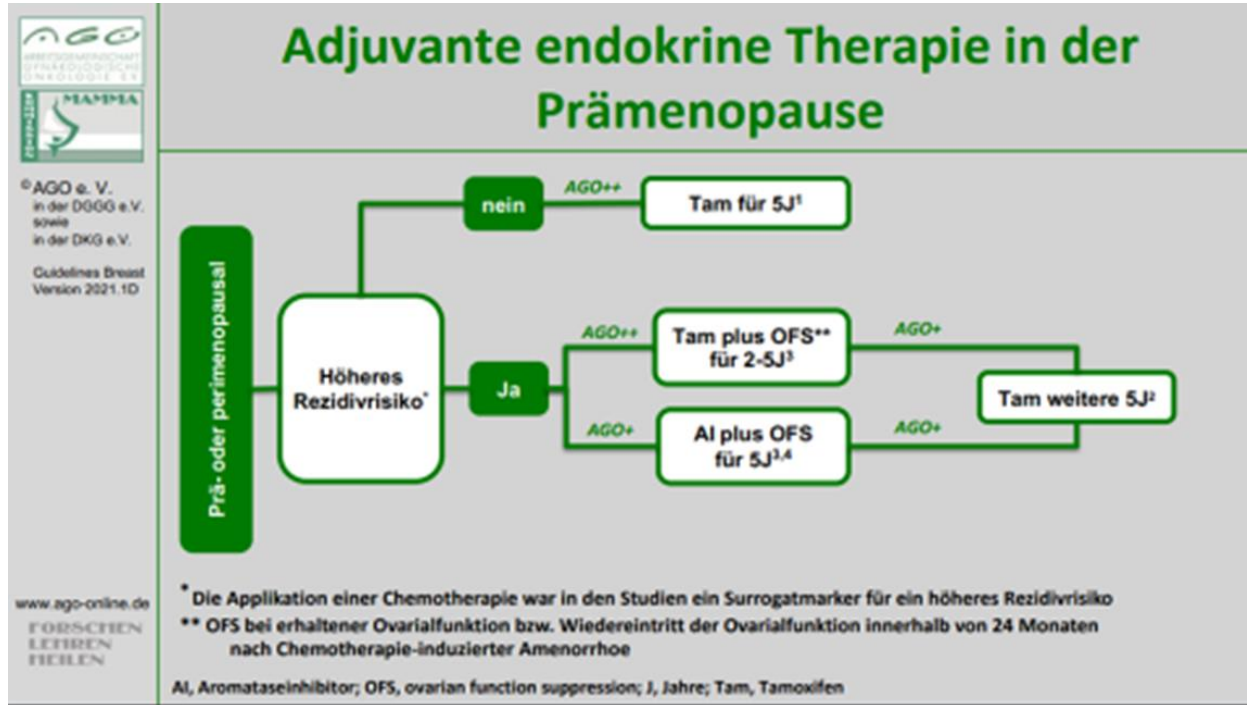
1:1

Trastuzumab deruxtecan  
(T-DXd; DS-8201)  
5.4 mg/kg q3w for  
14 cycles  
(n=800)

Trastuzumab emtansine  
(T-DM1)  
3.6 mg/kg q3w for  
14 cycles  
(n=800)



# HR+ HER2 negatives Mammakarzinom



## SOFT and TEXT 2 major questions:

In premenopausal women, does OFS add benefit and is AI better than Tamoxifen?

Enrolled: Nov03-Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo  
OR planned chemo

R  
A  
N  
D  
O  
M  
I  
Z  
E

TEXT (N=2672)

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

R  
A  
N  
D  
O  
M  
I  
Z  
E

SOFT (N=3066)

- Tamoxifen x 5y
- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

SOFT+TEXT  
Joint Analysis  
(N=4690)

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

Median follow-up 9 years

OFS=ovarian function suppression

Presented and modified with permission, Pagani and IBCSG, SABCs 2017

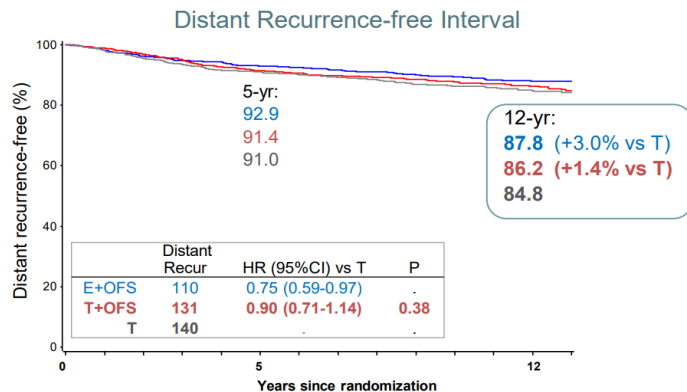


# Tam vs OFS + TAM

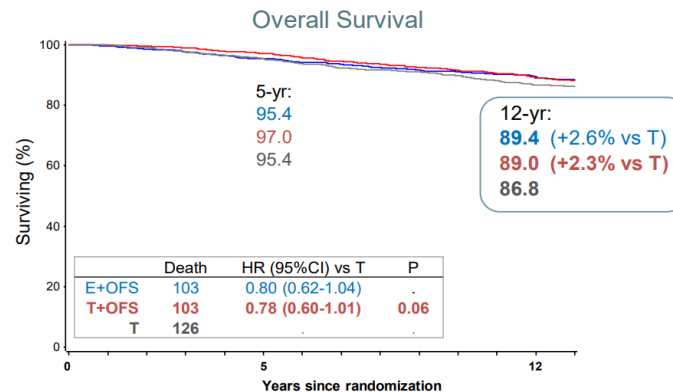
San Antonio Breast Cancer Symposium®, December 7-10, 2021

## OFS Question: SOFT Overall Population

35% LN+; 12 years median follow-up



	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	68	0.76 (0.55-1.04)	42	0.74 (0.50-1.12)
T+OFS:	83	0.93 (0.69-1.25)	48	0.85 (0.58-1.26)
T:	87	.	53	.
At risk:	3047 pts	13787 pyfu	2521 pts	16343 pyfu



	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	45	1.00 (0.66-1.51)	58	0.70 (0.50-0.98)
T+OFS:	29	0.63 (0.40-1.01)	74	0.86 (0.63-1.18)
T:	45	.	81	.
At risk:	3047 pts	14524 pyfu	2745 pts	18383 pyfu

T+OFS vs T: absolute reductions in distant recurrence and death 1.4% and 2.3% at 12 years

E+OFS vs T: absolute reductions in distant recurrence and death 3.0% and 2.6% at 12 years

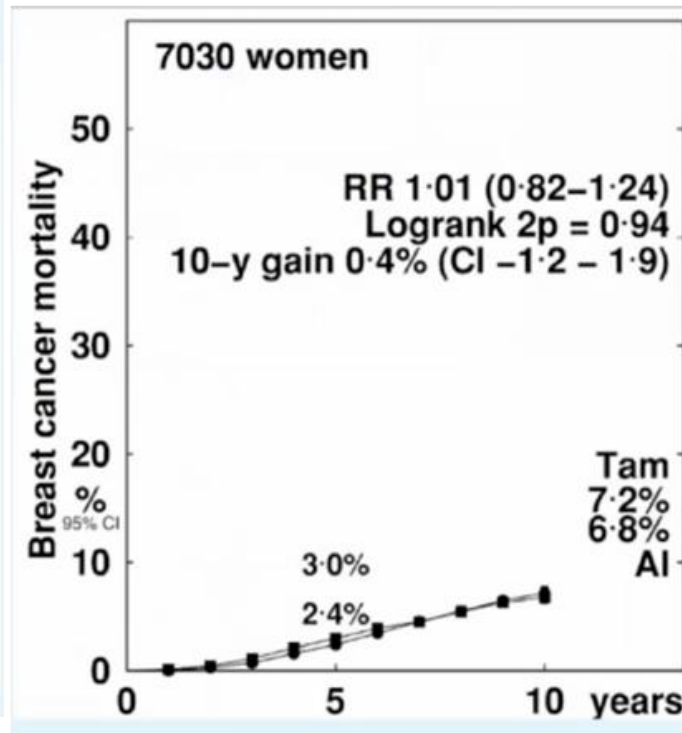
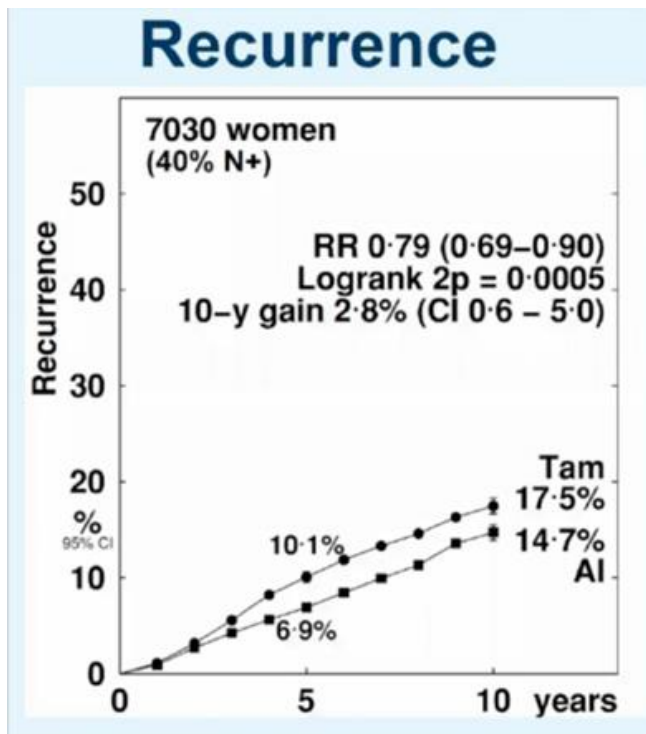
pyfu=person-years follow-up

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# OFS +Tam vs OFS + AI



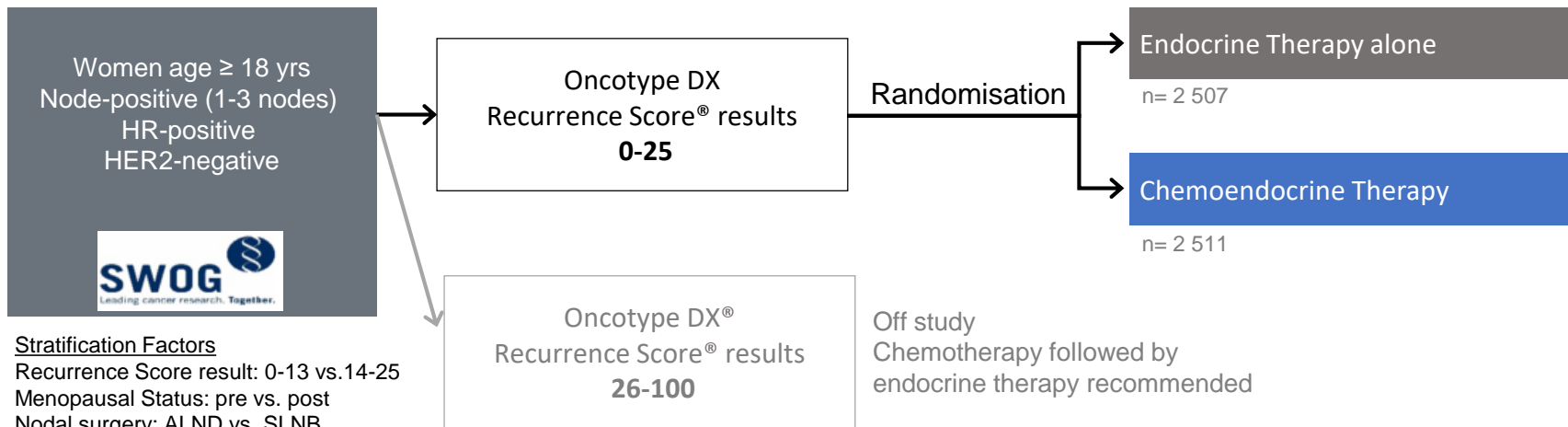
EBCTCG SABCS 2021



# Wer bekommt heutzutage keine Chemotherapie? Therapieindikation anhand von genomischen Signaturen

- postmenopausale Frauen mit Mammaprint low risk
- N0: postmenopausale Frauen  $RS < 25$ ;  
prämenopausale Frauen  $RS < 15$  (TAILORx)
- N1: postmenopausale Frauen  $RS < 25$   
(RxPONDER)
- N0-1  $RS 0-11$  und  $RS 12-25$  /endokrin sensibel  
❖ (ADAPT)

# RxPONDER was conducted to further refine chemotherapy benefit estimates in HR+, HER2-, N1 early-stage breast cancer patients



## Stratification Factors

Recurrence Score result: 0-13 vs. 14-25  
Menopausal Status: pre vs. post  
Nodal surgery: ALND vs. SLNB

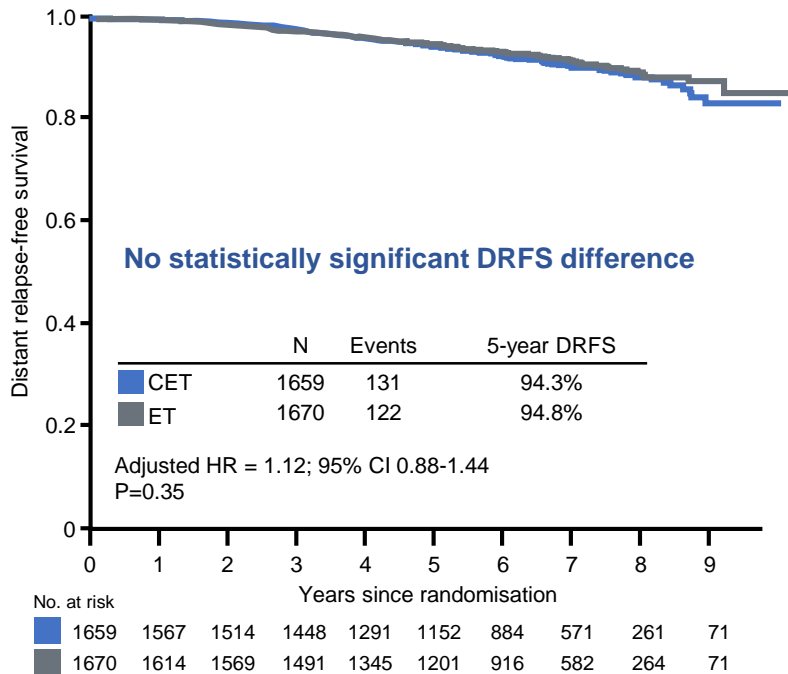
**Primary Objective: Determine the effect of chemotherapy, if any, in invasive disease-free survival in women with lymph node-positive disease and Recurrence Score<sup>®</sup> results 0-25, with adjustment for menopausal status**

# N1 premenopausal RS<sup>®</sup> results 0-25 women showed a benefit from chemotherapy in updated analysis with 6.1 years median follow up

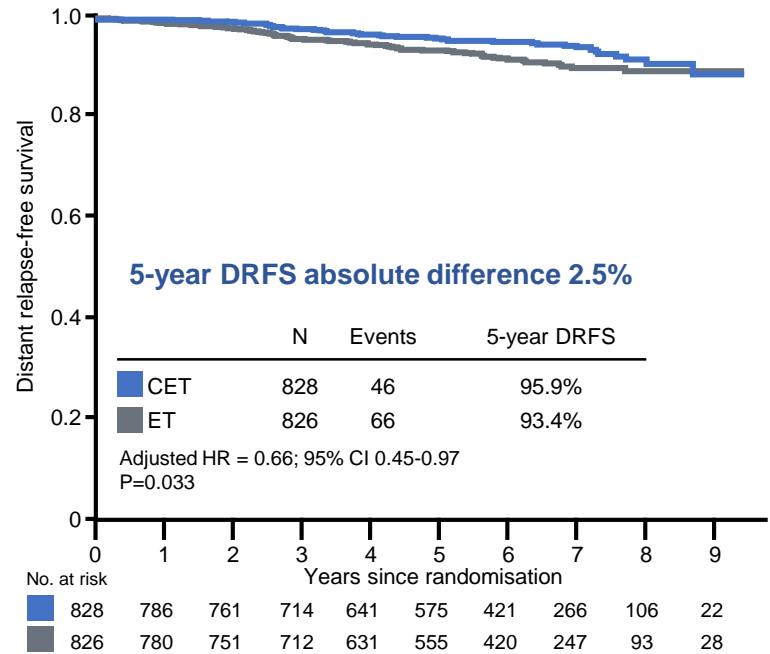
N1  
Postmenopausal

N1 Premenopausal RxPONDER  
Median follow up 6.1 years

## DISTANT RELAPSE-FREE SURVIVAL POSTMENOPAUSAL RS<sup>®</sup> RESULTS 0-25



## DISTANT RELAPSE-FREE SURVIVAL PREMENOPAUSAL RS<sup>®</sup> RESULTS 0-25

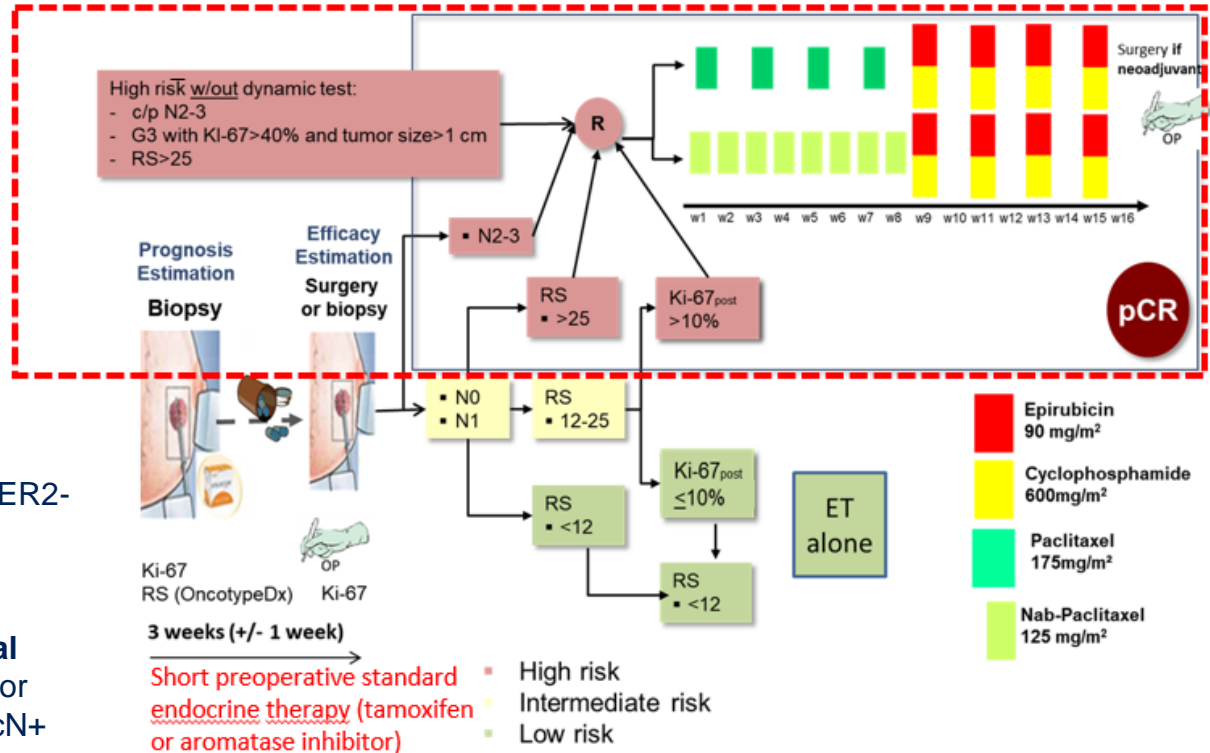


# WSG-ADAPT HR+/HER2-

(NCT01779206)

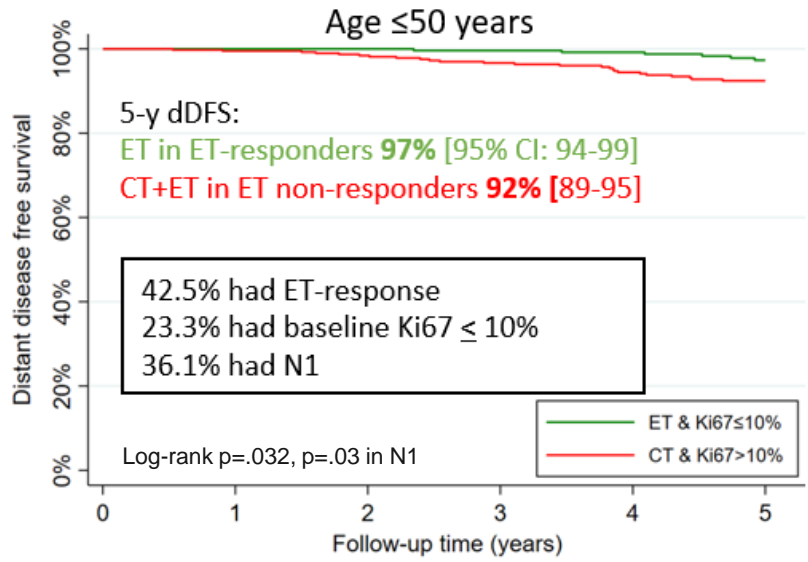
## Trial design

- Female patients >18 years
- ER and/or PR positive (>1%)/ HER2-negative unilateral EBC
- cT1-4c, cN0-3
- **Candidates for adjuvant chemotherapy by conventional prognostic criteria:** cT2 or G3 or Ki-67>15% or <35 years old or cN+

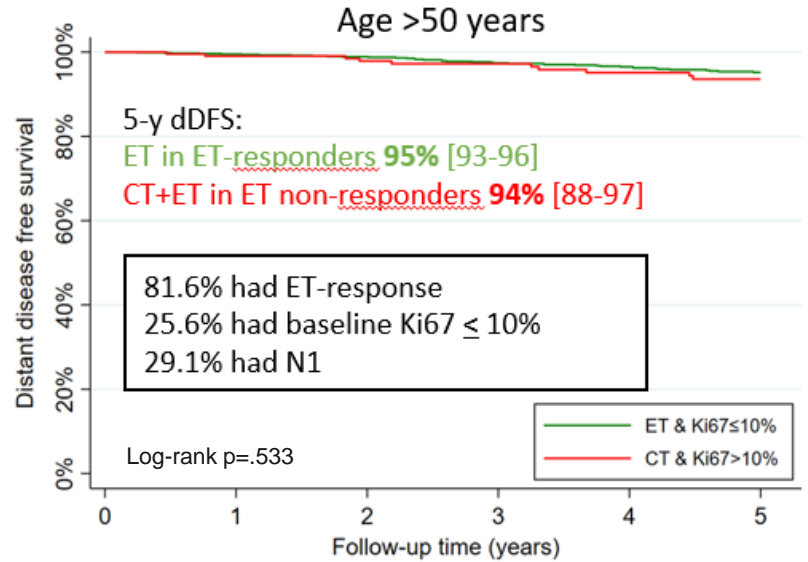


# WSG-ADAPT HR+/HER2- CT and ET Trial

## N0-1/RS 12-25: dDFS by trial in age subgroups (treatment allocated according to ET-response)



Number at risk		0	1	2	3	4	5
ET & Ki67 ≤ 10%	330	309	268	249	234	117	
CT & Ki67 > 10%	447	387	345	318	292	152	

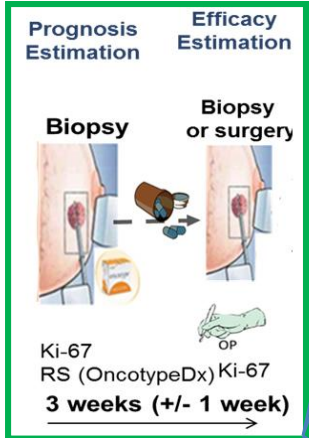


Number at risk		0	1	2	3	4	5
ET & Ki67 ≤ 10%	1084	982	845	780	719	367	
CT & Ki67 > 10%	243	197	161	139	128	72	



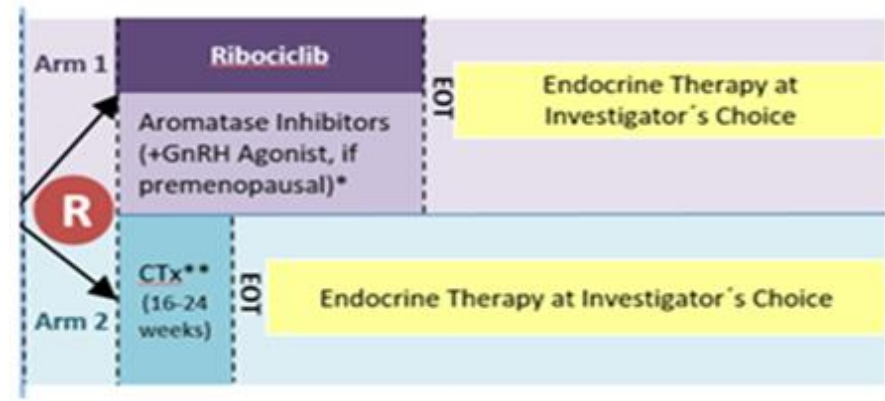
Intermediate to high risk HR+/HER2- breast cancer

Genomic signature (Oncotype Dx)



Pre/postmenopausal N2-3	RS 0-25	ET-sensitive biology
Pre/postmenopausal N0-1	RS $\geq 26$	ET-sensitive biology
Premenopausal N0	RS 16-25	+/- ET-insensitive or unknown
Premenopausal N1	RS 0-25	+/- ET-insensitive or unknown
Postmenopausal N0-1	RS 0-25	Very high risk e.g. ET-insensitivity and high tumor burden

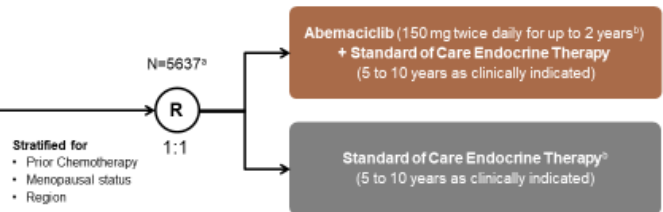
ET-sensitivity assessment according to ER/PR high and/or low Ki-67



# Perspektiven HR+/HER2-

**HR+, HER2-, high risk early breast cancer**  
**High risk defined as**

- $\geq 4$  positive axillary lymph nodes (ALN) or
- 1–3 ALN and at least 1 of the below
  - Tumour size  $\geq 5$ cm
  - Histologic grade 3
  - Centrally tested Ki67  $\geq 20\%$



**Stratified for**

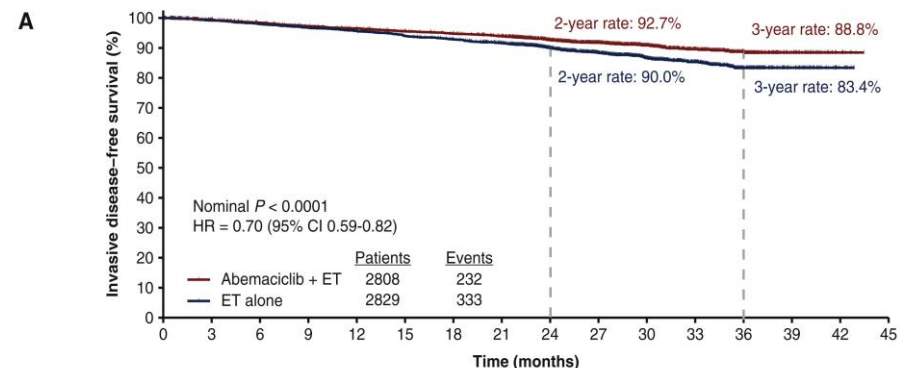
- Prior Chemotherapy
- Menopausal status
- Region

- Other criteria**
- Women or men
  - Pre-/ postmenopausal
  - With or without prior adjuvant/neoadjuvant Chemotherapy
  - No distant metastases

**Endocrine therapy** of physician's choice

**Primary objective:** Invasive disease-free survival (STEEP criteria)

**Key Secondary Objectives:** Distant relapse-free survival, Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

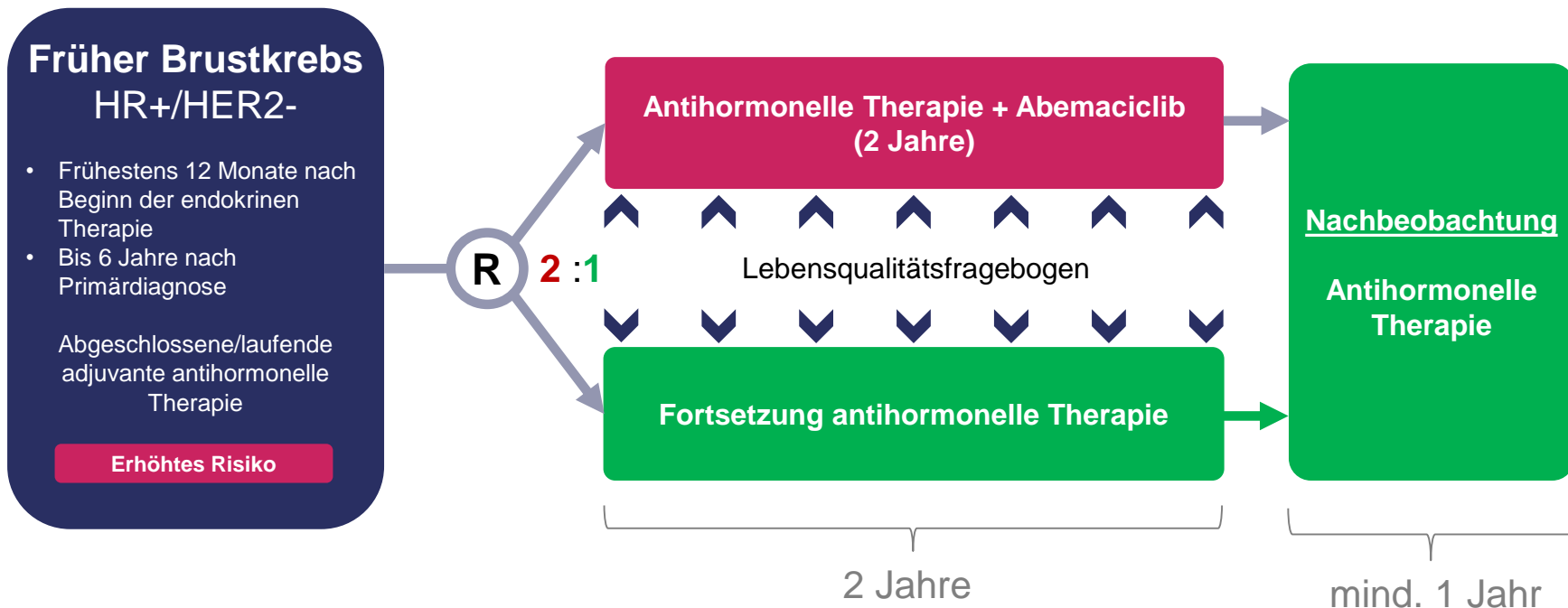
**Menopausal status**

Premenopausal	1221	85	1232	142		0.58 (0.44-0.76)
Postmenopausal	1587	147	1597	191		0.79 (0.64-0.98)

0.082







**Herzlichen Dank für Ihre Aufmerksamkeit**

**Bleiben Sie gesund !**

**Bitte denken Sie an unseren workshop  
„orale Therapie (CDK 4/6,PARPi)“  
im April**

