

Prämenopausales hormonrezeptorpositives Mamma- karzinom: Was ist die optimale adjuvante Therapie ?

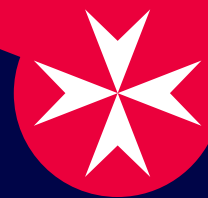
BKK 2022

Ulrike Nitz

Brustzentrum Niederrhein



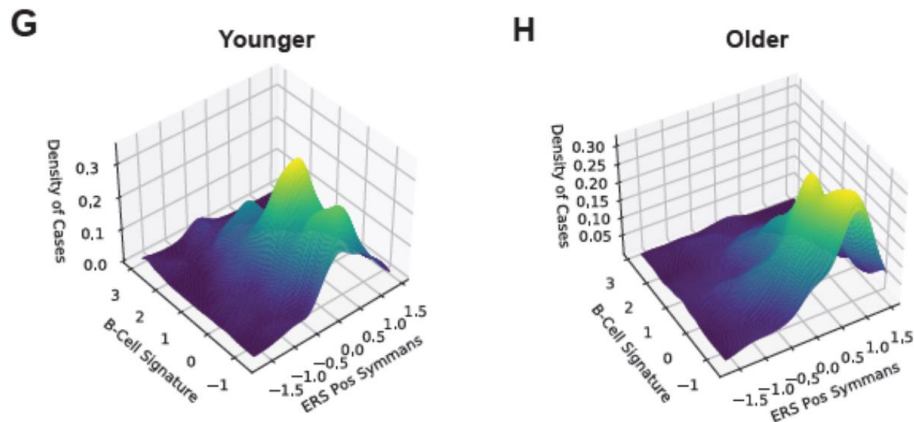
JOHANNITER



Allgemeines : Genprofile in Prä und -Postmenopause:

Different Genes are Expressed in Younger vs older Patients

Overall younger women had a higher immune gene expression that likely makes them more chemotherapy sensitive and lower ER-associated genes that could make them less endocrine sensitive



Pusztai L et al. JNCI under review - with courtesy from Lajos Pusztai



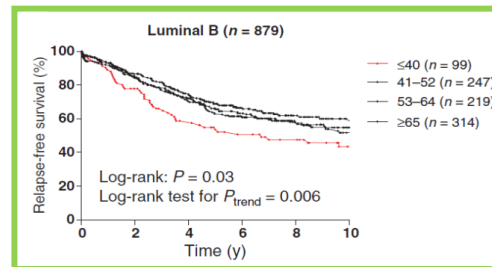
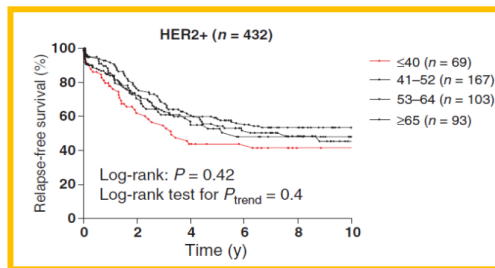
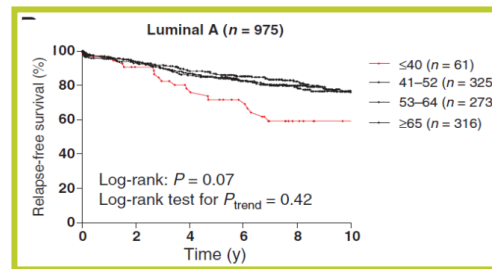
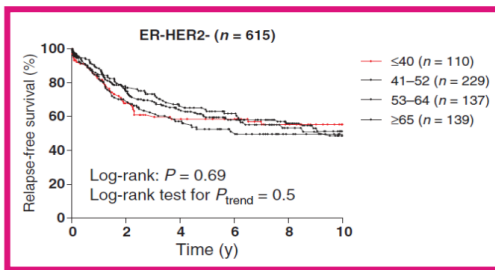
Allgemeines: Alter als unabhängiger Prognosefaktor (subtypenspezifisch)

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

Importance of age differs by biological subtype

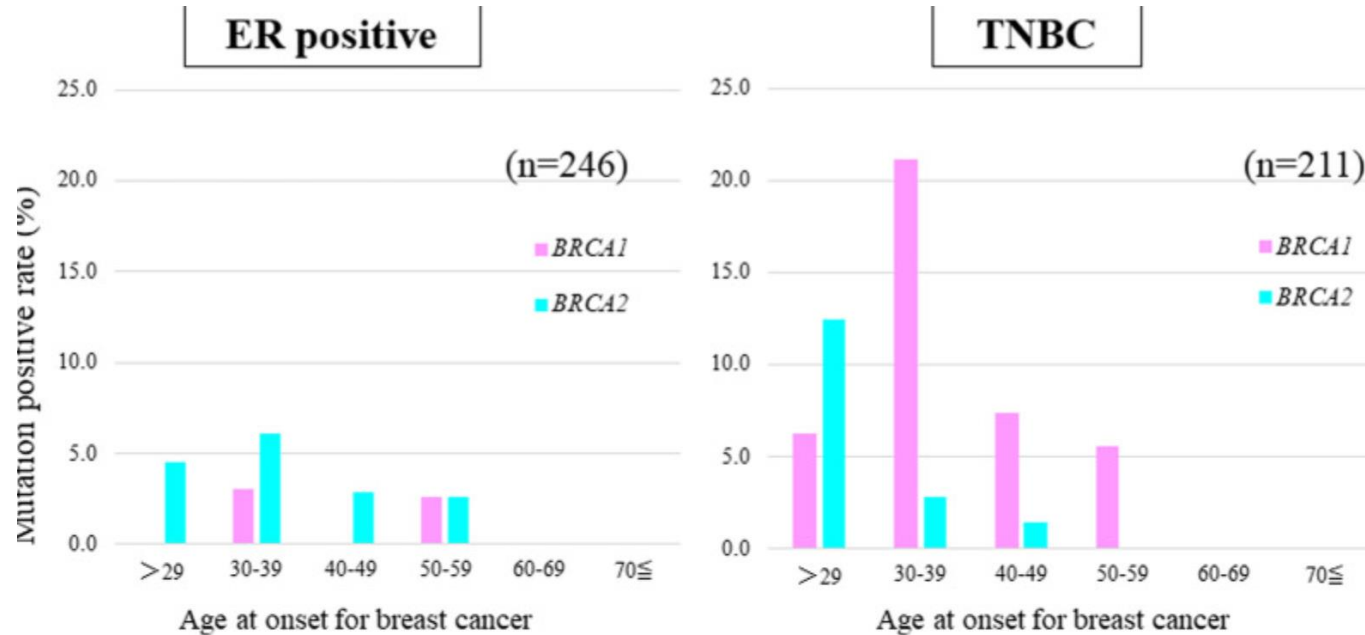


Azim HA Jr, et al. *Clinical Cancer Res* 2012;18:1341-51



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Allgemeines: Wahrscheinlichkeit der BRCA1/2 Mutation in Abhängigkeit vom Alter



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



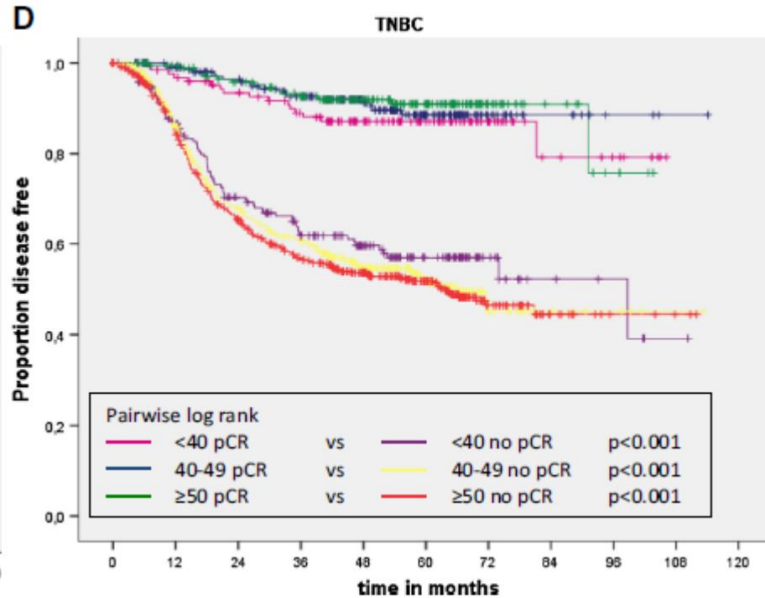
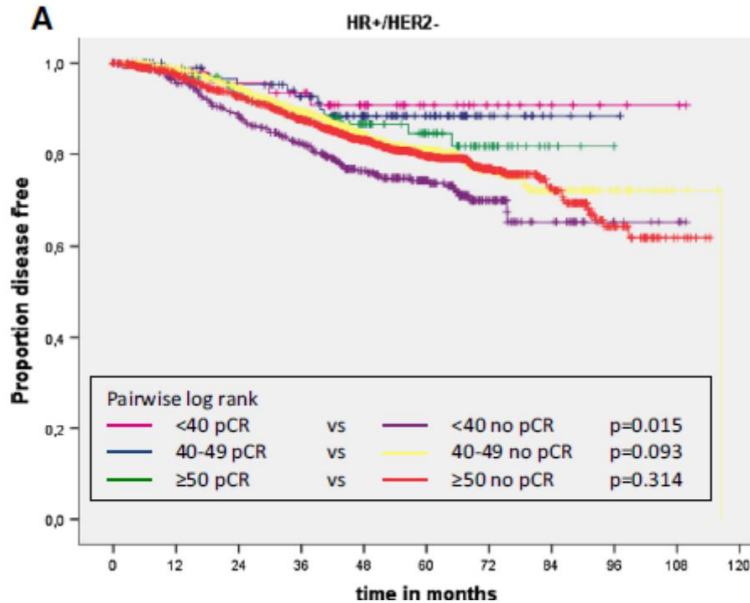
Allgemeines: Bedeutung von pCR/non pCR altersabhängig

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pCR effect on DFS only in young women with HR+ bc.



Loibl S et al. Breast Cancer Res Treat 2015

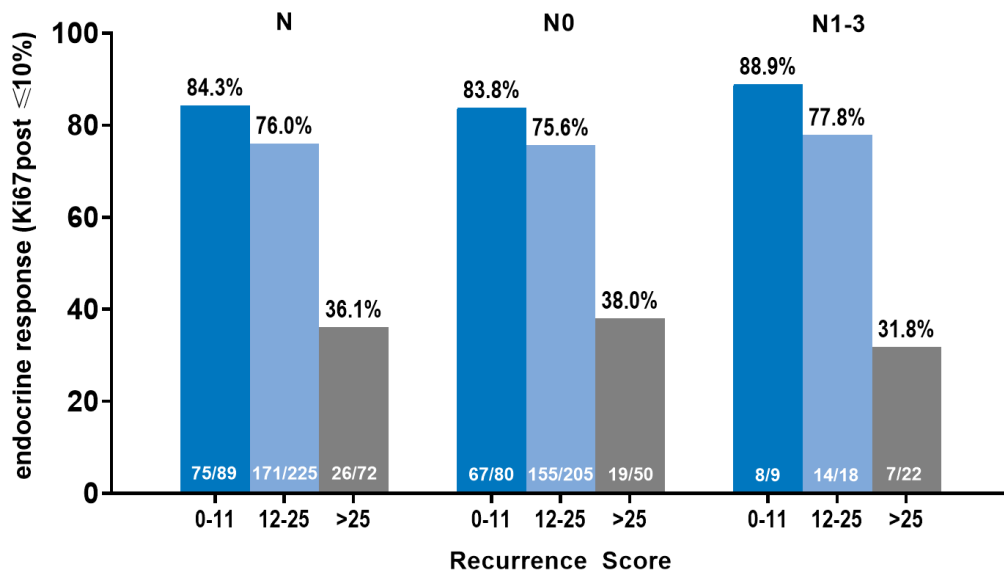


pCR bei <40, 40-49 und ≥ 50 Jahre : 20.9%, 17.7% und 13.7%



ADAPT HR+/HER2-

Endocrine response (Ki67_{post} ≤10%) in run-in phase¹



ADAPT updated analysis:

59.9% ET responders

78.1% AI group (postmenopausal)

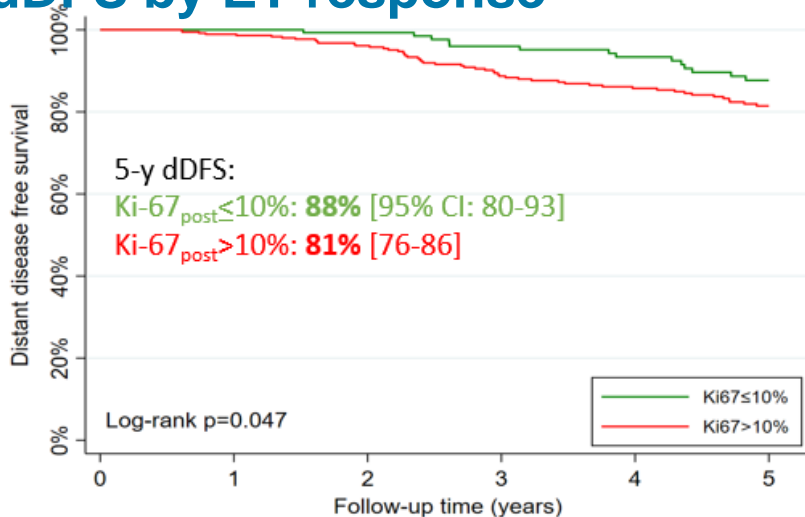
41.1 % Tam group (premenopausal)

¹Nitz et al, Ther Adv Med Oncol, 2020

WSG-ADAPT HR+/HER2- CT Trial

RS>25 cohort, any N, any ET-response

dDFS by ET-response



Number at risk	0	1	2	3	4	5
Ki67≤10%	182	158	125	115	105	53
Ki67>10%	408	345	287	245	221	107

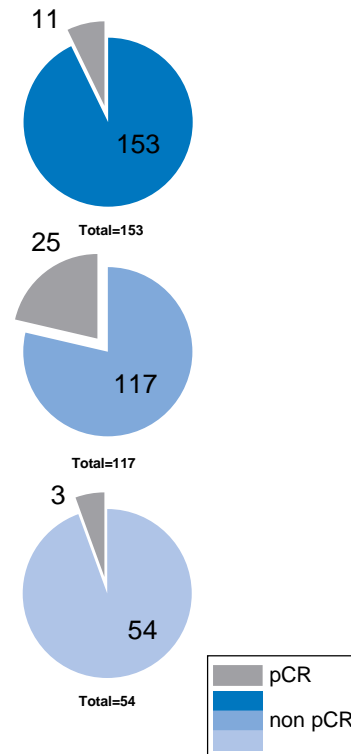
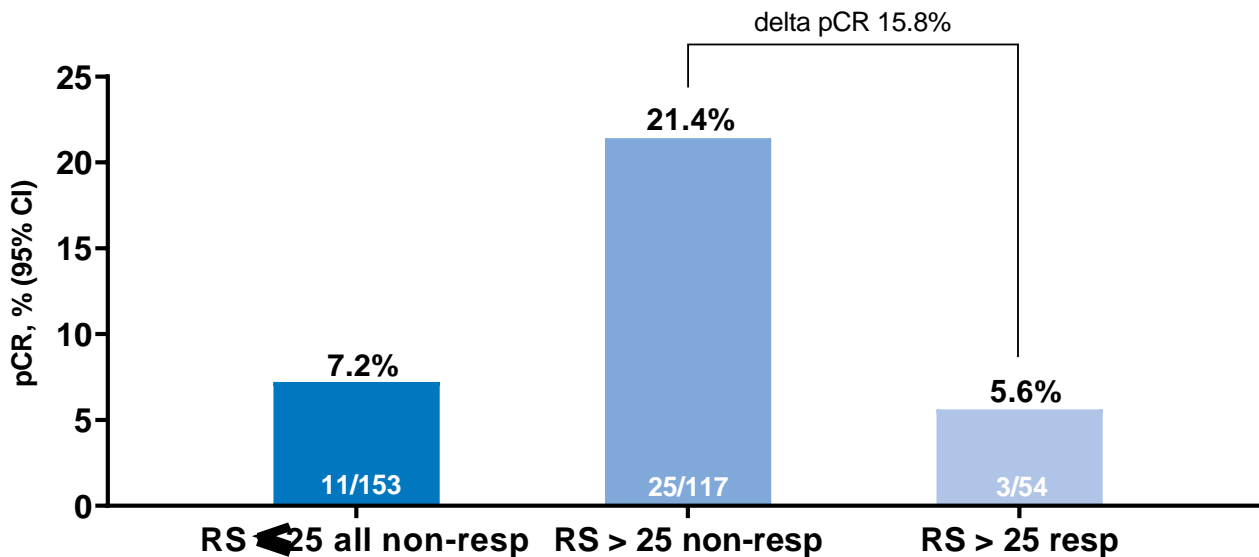
Multivariable analysis for dDFS*

Coding	Hazard Ratio	95% CI	P
Ki67 _{post} ≤ 10% vs. Ki67 _{post} > 10%	0.42	0.20, 0.87	0.02
Tumor size > 2 cm vs. ≤ 2 cm	2.56	1.40, 4.66	0.002
N0 (reference)	1		
N1	1.36	0.77, 2.39	0.292
N2-3	2.13	0.98, 4.63	0.058
PR (per 10% increase)	0.92	0.84, 1.00	0.057

*adjusted for RS (by unit) and Ki67_{post}/Ki67_{baseline}



ADAPT HR+ /HER2- pCR by Recurrence Score and ET- response



Zusammenfassung Allgemeines

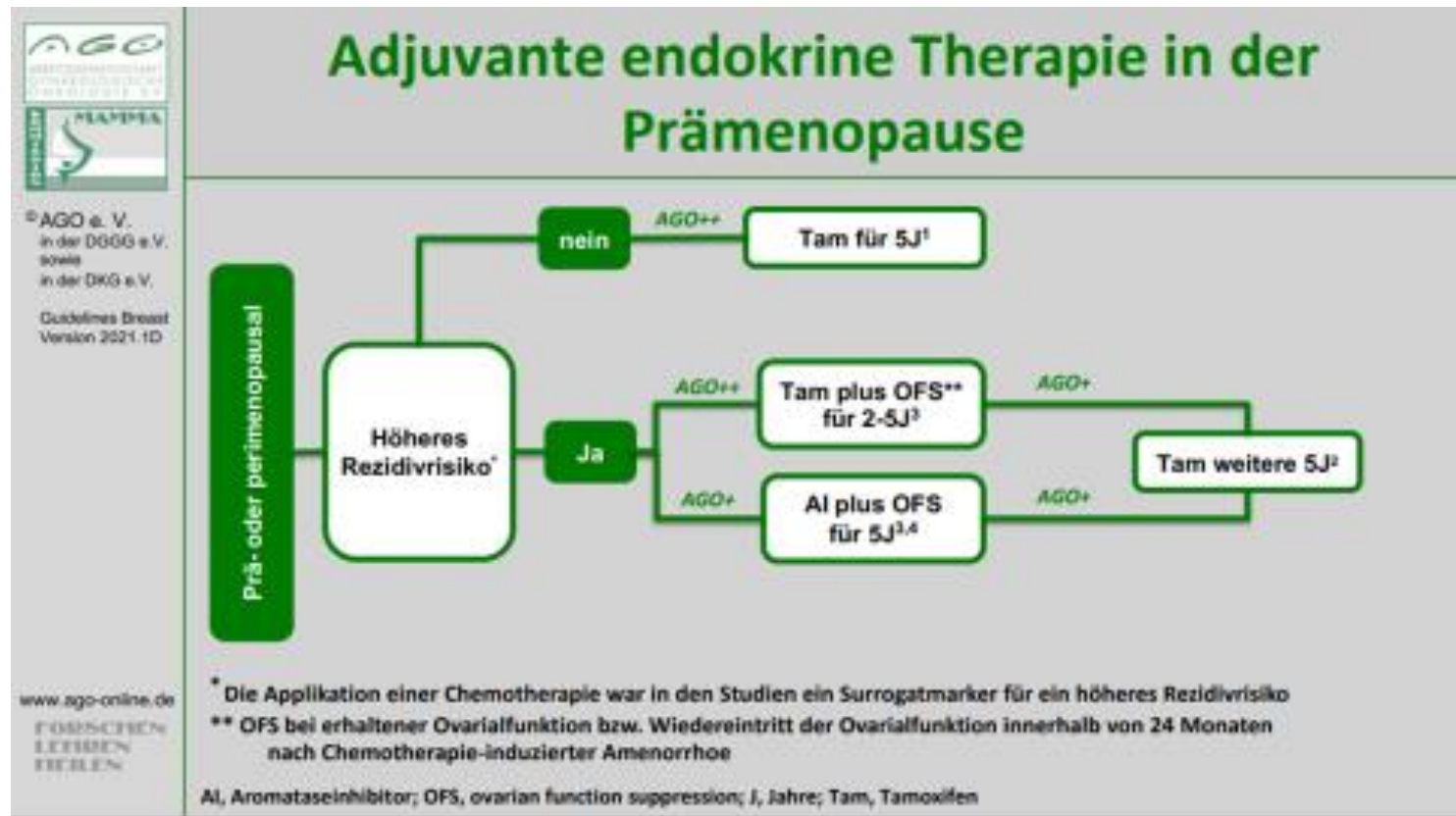
- Prä und postmenopausale Tumore sind biologisch unterschiedlich
- Alter ist ein unabhängiger Prognosefaktor
- BRCA 1/2 Mutationen sind bei sehr jungen Patientinnen häufiger (Testung wird erstattet bei Erkrankung vor dem 36. Geburtstag)
- Ki 67 post scheint eine bedeutende Rolle zu spielen (prädiktiv für ET als auch prognostisch für Cht)

→ Risikoabwägung anhand von Tumogrösse, Grading, Lymphknotenbefall, Ki-67, Alter

→ „Prädiktion“ anhand von Ki-67 post / Recurrence score



Endokrine Therapie



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

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TEXT (N=2672)

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

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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



Patient Characteristics

	SOFT No chemo (N=1419)	SOFT Prior chemo* (N=1628)	TEXT No chemo (N=1053)	TEXT Chemo (N=1607)
<i>Median age</i>	46	40	45	43
Age <35 yrs	1%	20%	4%	12%
LN +	9%	57%	21%	66%
T-size >2cm	14%	47%	19%	53%
Grade 3	7%	34%	11%	37%
HER2 +	4%	19%	5%	17%
Surgery to random. (median)	1.8 mo	8.0 mo	1.5 mo	1.2 mo

*20% of chemotherapy receipt involved neoadjuvant administration



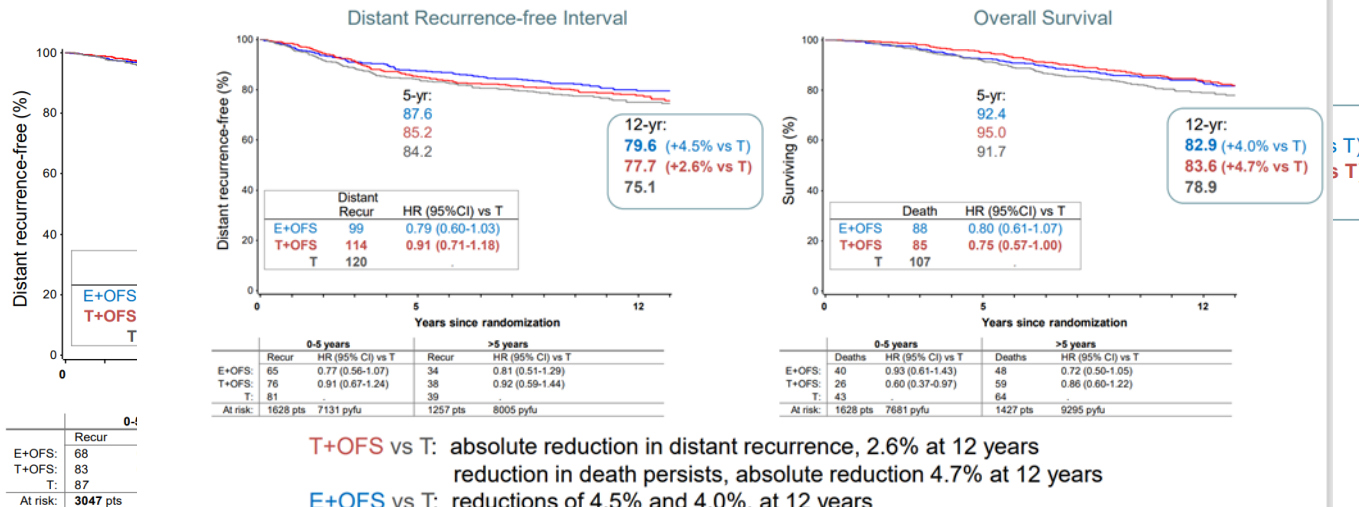
Tam vs OFS + TAM

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

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SOFT Prior Chemotherapy Cohort

57% LN+; 12 years median follow-up



pyfu=person-years follow-up

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T+OFS vs T: absolute reductions in distant recurrence and death 4.5% and 2.5% at 12 years

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

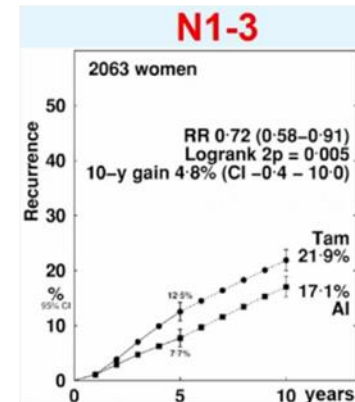
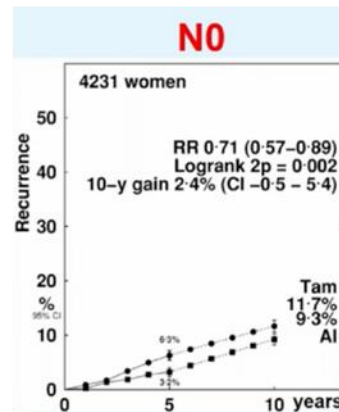
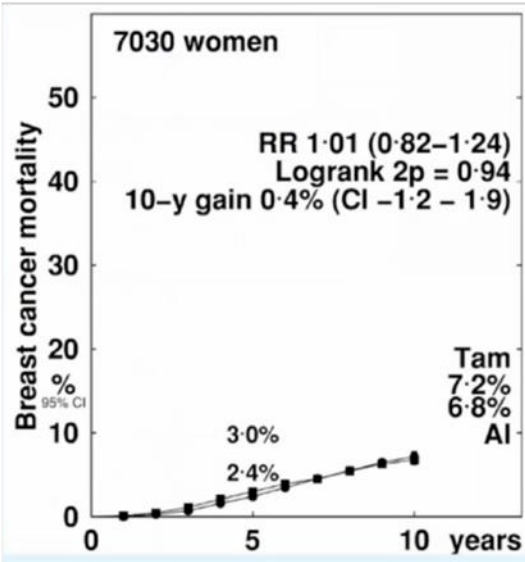
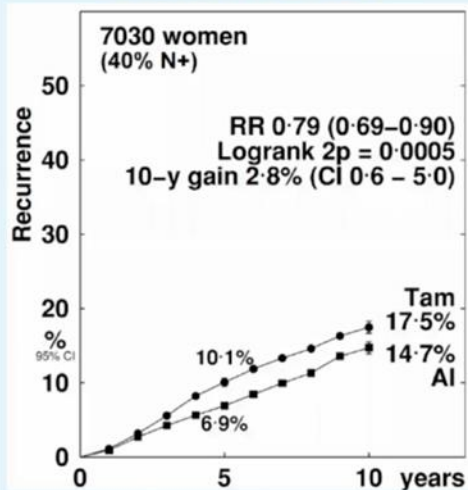
pyfu=person-years follow-up

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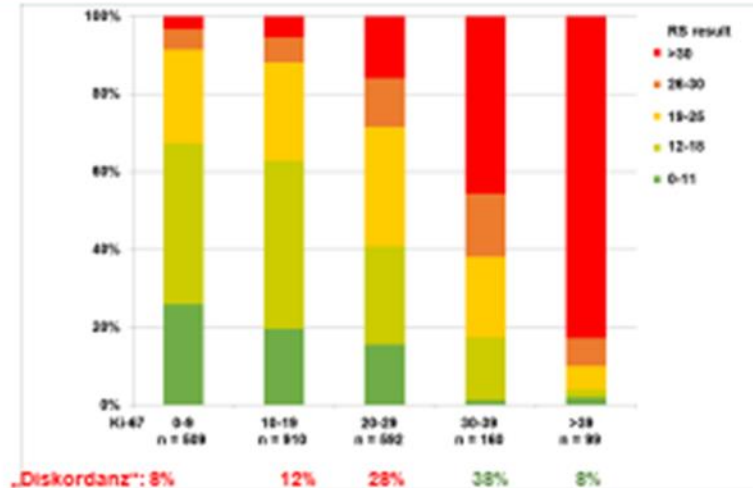
OFS: Tam vs AI

Recurrence



Biomarkergesteuerte Chemotherapieindikation HR+/HER2 neg und N0-1: genomische Signatur ja/nein?

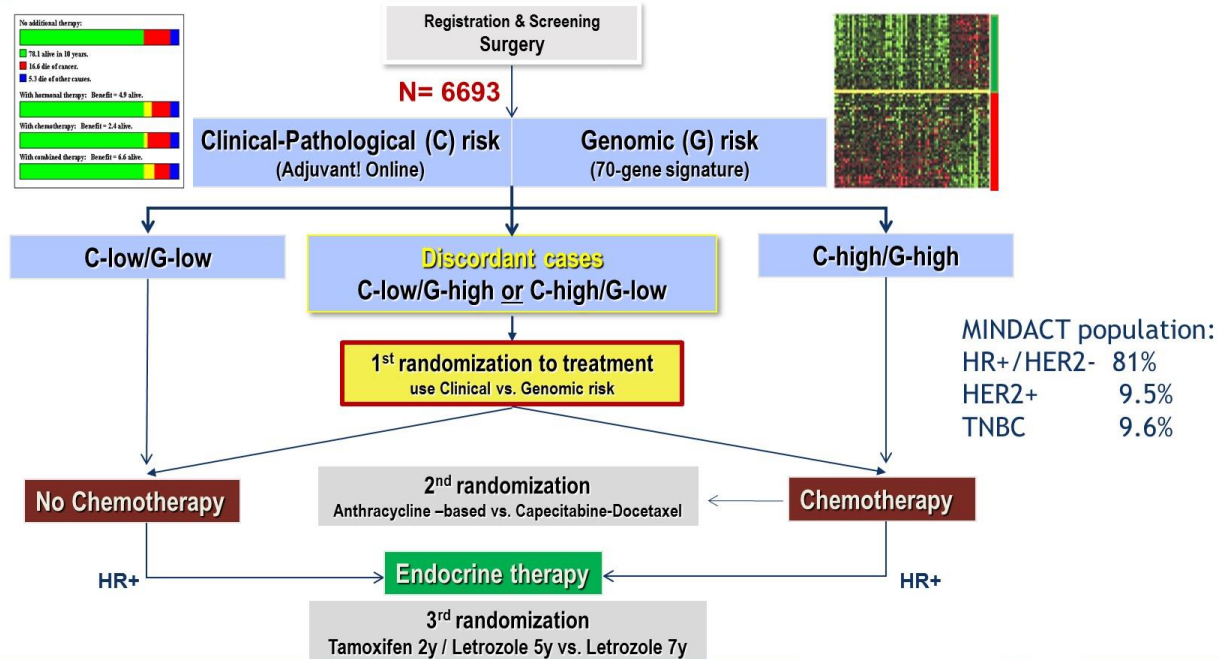
PlanB: Recurrence Score by (central) Ki-67



Biomarkergesteuerte Chemotherapieindikation HR+/HER2 neg und N0-1: Mammaprint



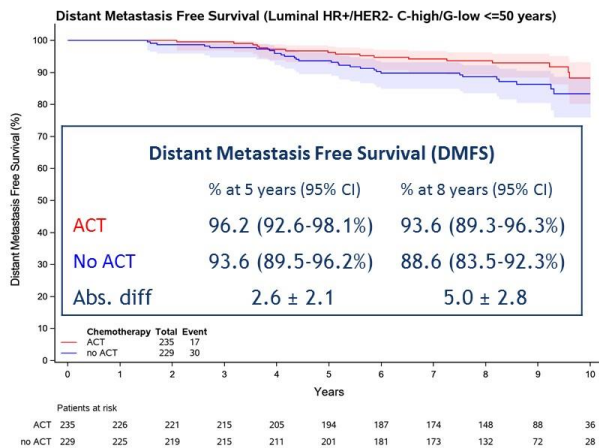
MINDACT TRIAL DESIGN



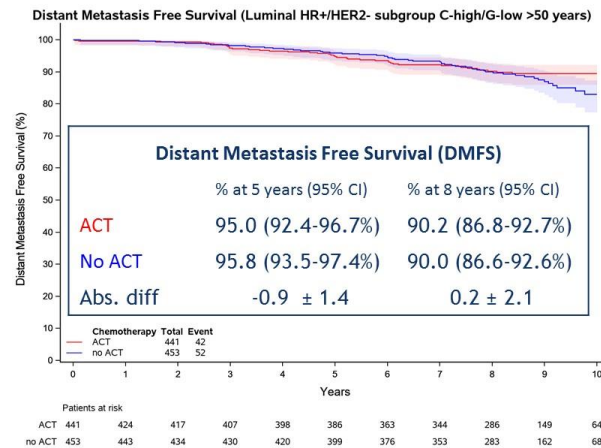
DMFS in C-High / G-Low risk patients with luminal cancers (HR+/HER2-) stratified by age ITT population

Age ≤50 years

Age >50 years



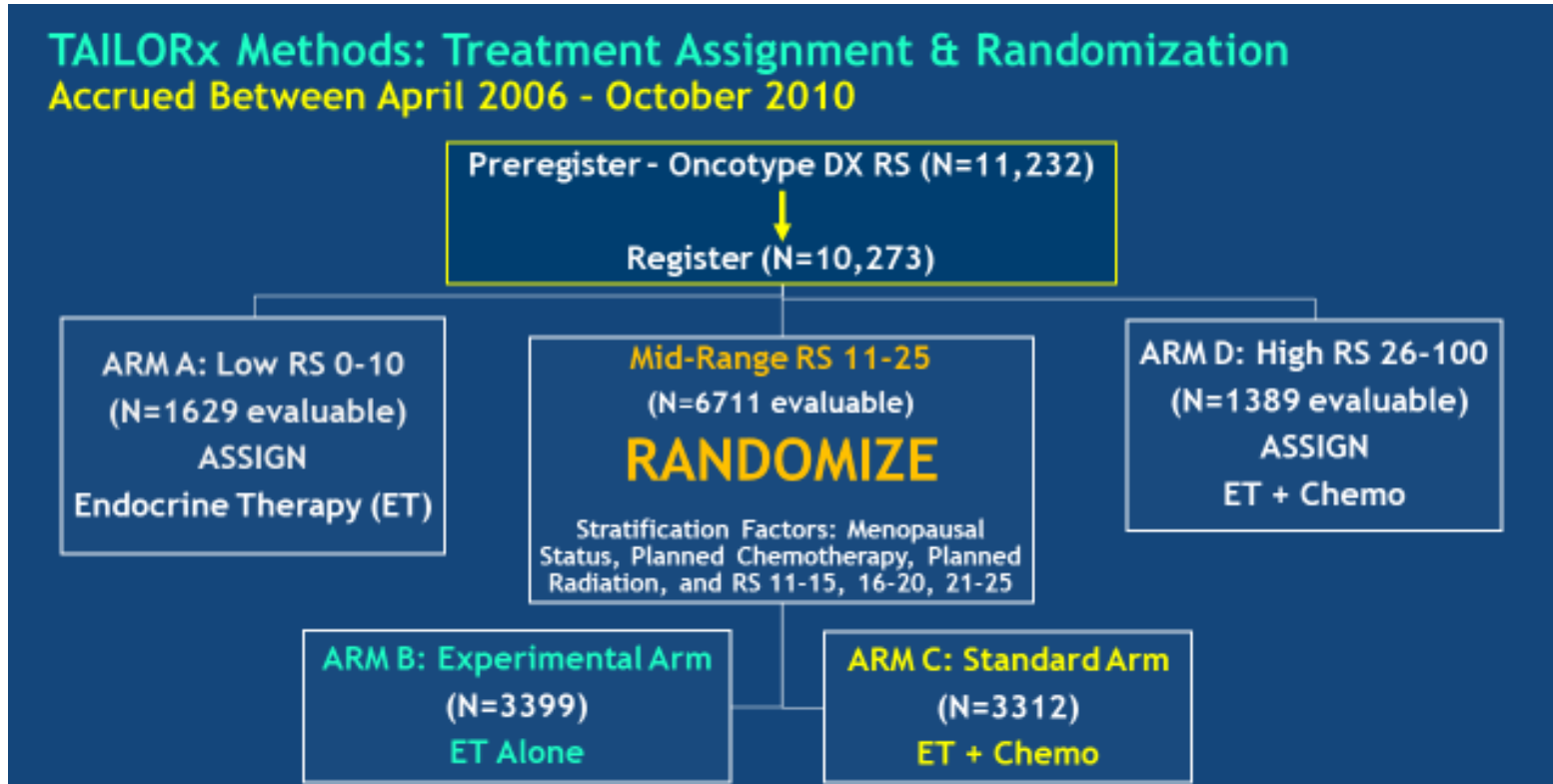
5% difference



NO difference

Biomarkergesteuerte Chemotherapieindikation HR+/HER2 neg und N0 und N1: Oncotype DX

TAILORx Methods: Treatment Assignment & Randomization Accrued Between April 2006 - October 2010



N0- TailorX

Total patients	RS® 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
n=9719	n=1619	n=2373	n=2712	n=1626	n=1389
Age >50 years n=6665 (69%)	No CT Benefit n=1190 (12%)	No CT Benefit n=1572 (16%)	No CT Benefit n=1789 (18%)	No CT Benefit n=1134 (12%)	CT Benefit n=980 (10%)
Age ≤50 years n=3054 (31%)	No CT Benefit n=429 (4%)	No CT Benefit n=801 (8%)	~1.6% CT Benefit n=923 (9%)	~6.5% CT Benefit n=492 (5%)	CT Benefit n=409 (4%)

Patients ≤50 years	
Low clinical risk	7% of all patients No CT benefit
High clinical risk	2% of all patients ~6.5% CT benefit
	3% of all patients ~6.4% CT benefit
	2% of all patients ~8.7% CT benefit

RxPONDER Schema

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR $\geq 1\%$, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

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Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy
Recommended

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N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

Stratification Factors

Recurrence Score: 0-13 vs. 14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

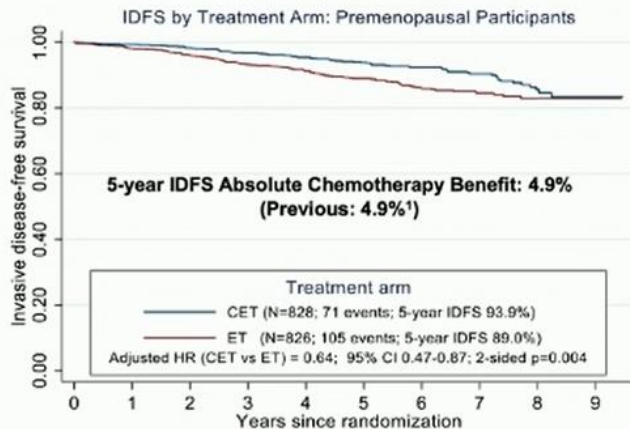
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

RxPONDER update Dec-21

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

Updated Analysis: Premenopausal Women Have Chemotherapy Benefit

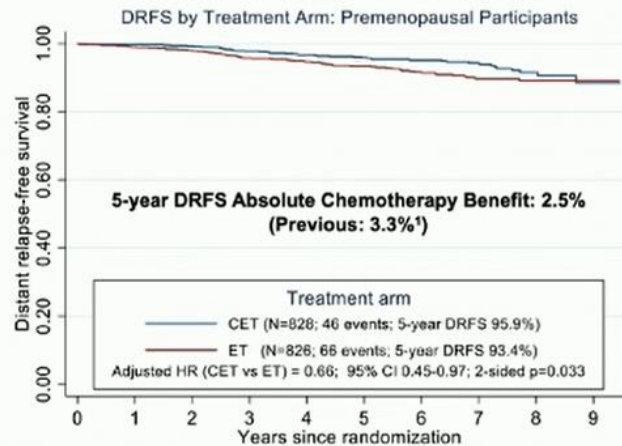
Invasive Disease-Free Survival



Number at risk

CET	828	783	754	706	632	561	408	252	99	21
ET	826	774	737	694	610	533	398	236	86	27

Distant Relapse-Free Survival



Number at risk

CET	828	786	761	714	641	575	421	266	106	22
ET	826	780	751	712	631	555	420	247	93	28

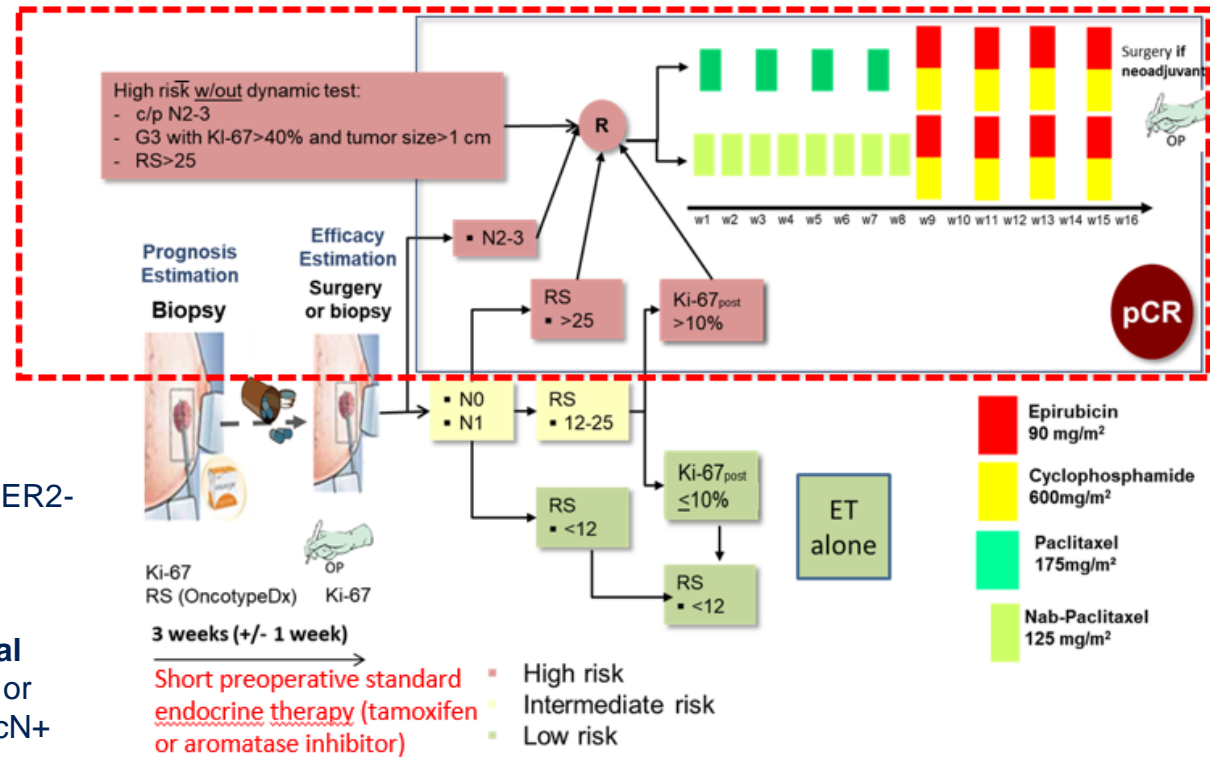
¹ Kalinsky et al, New England Journal of Medicine: December 1, 2021

WSG-ADAPT HR+/HER2-

(NCT01779206)

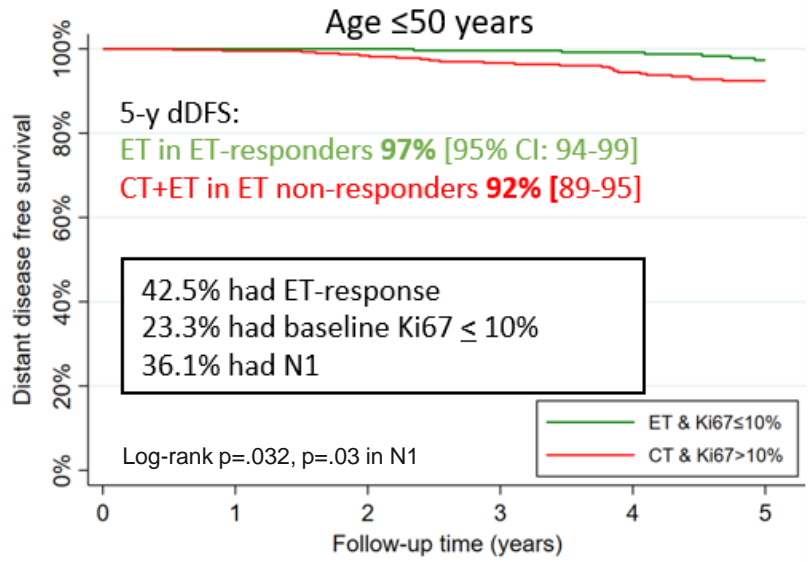
Trial design

- 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+

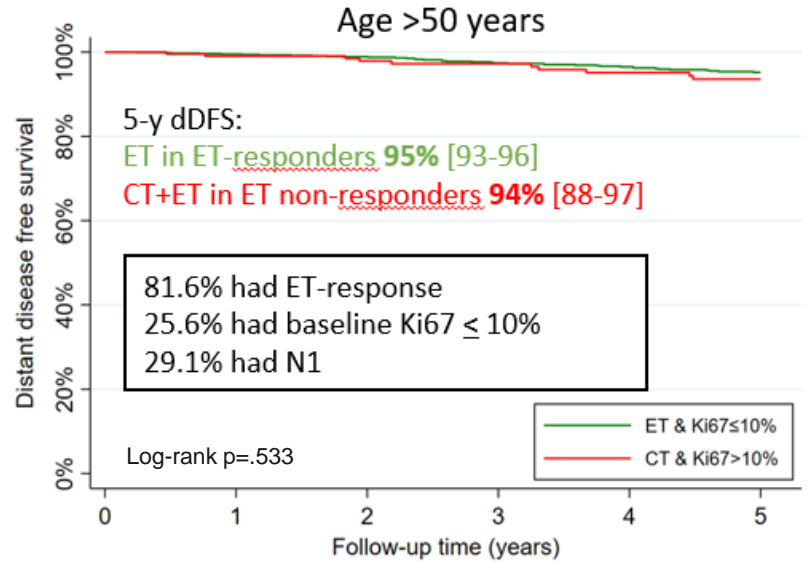


WSG-ADAPT HR+/HER2- CT and ET Trial

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	



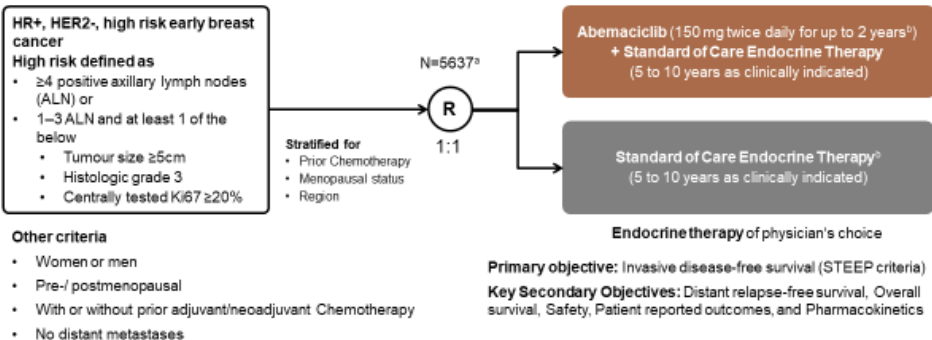
Number at risk		0	1	2	3	4	5
ET & Ki67 ≤ 10%	1084	982	845	780	719	367	
CT & Ki67 > 10%	243	197	161	139	128	72	

Zusammenfassung

- Mammaprint low risk/clinical high risk : ! Chemotherapienutzen in der Prämenopause
- N0/ RS 0-15 kein Chemotherapienutzen (TAILORx) in der Prämenopause
- N1 /RS 0-25 Chemotherapienutzen in der Prämenopause (ddfs benefit 2.5% RxPONDER)
- (N1 /RS 0 - 11 kein Chemotherapienutzen (Plan B))
- N0-1 RS 0-11 excellent outcome (97.4% ddfs im ADAPT control arm) bei ≤ 50 jährigen
- N0-1/Ki67 post $\leq 10\%$ / RS 12-25 excellent outcome (97% ddfs) bei ≤ 50 jährigen

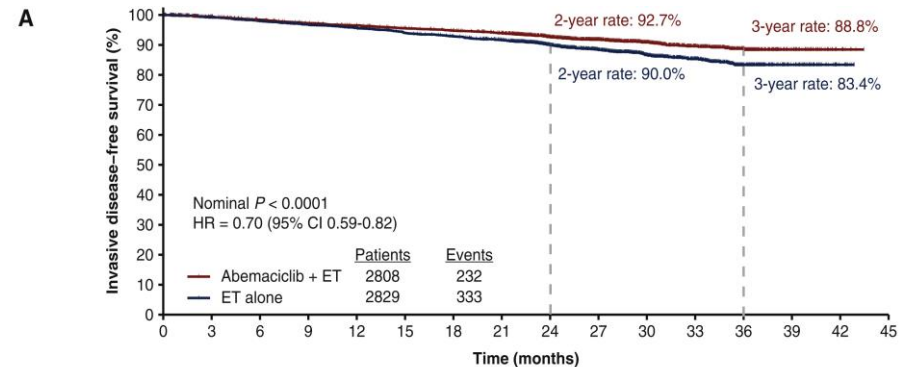


Perspektiven



Other criteria

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



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

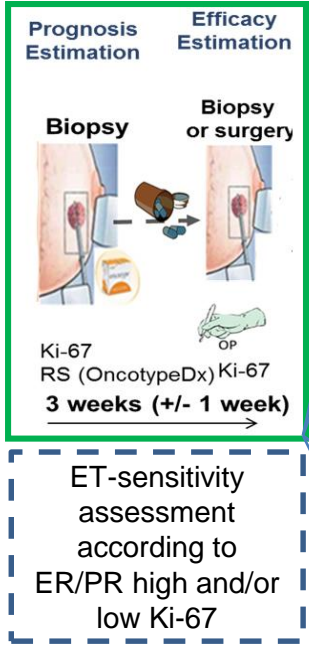
Menopausal status											0.082
Premenopausal	1221	85	1232	142							0.58 (0.44-0.76)
Postmenopausal	1587	147	1597	191							0.79 (0.64-0.98)





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

